The Assembly of Integrated Continuous Flow Platform for on-demand Rosiglitazone and Pioglitazone Synthesis

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1. General

Material and method used in experiments.

Most of the reagents and chemicals are bought from Spectrochem, AVRA, and Sigma-Aldrich, which were used as such without any further purification. Common organic chemicals and salts were purchased from AVRA chemicals, India. The water used was deionized water (18.2 mS conductivity) in the experiments. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using analytical chromatography silica gel 60 F254 pre-coated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). PTFE (id = 100-1000 μm) tubing, T-junction and back-pressure controller (BPR) were procured from Upchurch IDEX HEALTH & SCIENCE. HPLC Pump used was from KNAUER. SS318 capillary bought from the spectrum market, Mumbai, India. The heating reactor used was from the Thales Nano Nanotechnology, Inc.

Measurement method.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 600, 500, 400, or 300 MHz in $CDCl_3$ or DMSO-d_6 solvent. Chemical shifts for ^1H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet), coupling constant (Hz), and integration. For scanning electron microscopy (SEM), gold sputter coating was carried out on desired samples at a pressure ranging between 1 and 0.1 Pa. Sample was loaded in the chamber of JSM-7610F and recorded by operating at 10-2 to 10-3 Pa with EHT 15.00 kV with 300 V collector bias. LC-

MS was conducted on Shimadzu technology LCMS-8040 instrument equipped with LUNA C8 (250 □ 4.6 mm, 5.0u) and in build triple quadrupole detector. GC/MS analysis was conducted on Shimadzu technology GCMS-QP2010 instrument equipped with an HP-5 column (30 m × 0.25 mm, Hewlett-Packard) and inbuilt MS 5975C VL MSD system with triple-axis detector. Sonication (Power-Sonic 405) was used for washing the metal surface. ATR analysis was conducted on Portable FTIR spectrometer Bruker ALPHA. High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD instrument (DART) and Thermo Fisher Scientific Exactive (APCI). Datalog model DCS-PS-6401 power supply system was used to supply the constant current. Han's Yueming laser series (model CMA0604-B-A, Carbon dioxide based, laser power 80W) equipment was used for the fabrication of the micro-channel.

2. Optimization for the continuous flow production of Rosiglitazone intermediate 3.

*Reaction optimization condition***.** A stock solution of compound **1** in compound **2** was charged in a syringe and passed through SS-tubing reactor (reactor volume varied) using a pump at various flow rates, temperatures, and pressures. Optimization conditions were varied depending on the nature of the reagent, residence time, temperature, and pressure, etc. (Table 1).

*Optimized condition for semi-continuous production of Rosiglitazone intermediate **3**:* A stock solution of compound **1** (2-chloropyridine) (6.3 M) in compound **2** (2-(methylamino) ethanol) was charged in a syringe, and then passed through the combination of 20 mL SS-tubing reactor (1/16 inch OD tubing id 1 mm) and 45 mL SS-tubing reactor (1/8 inch OD tubing id 2 mm) (total reactor volume = 65 mL) with a flow rate of 2.7 mL/min. for the nucleophilic substitution reaction to occurs with the residence time 24 min., 220 °C temperature, 32 bar pressure (Table 1, Entry 13) (Figure S1). The resulting solution was quenched with cold water and extracting through the regular known prior art batch process.

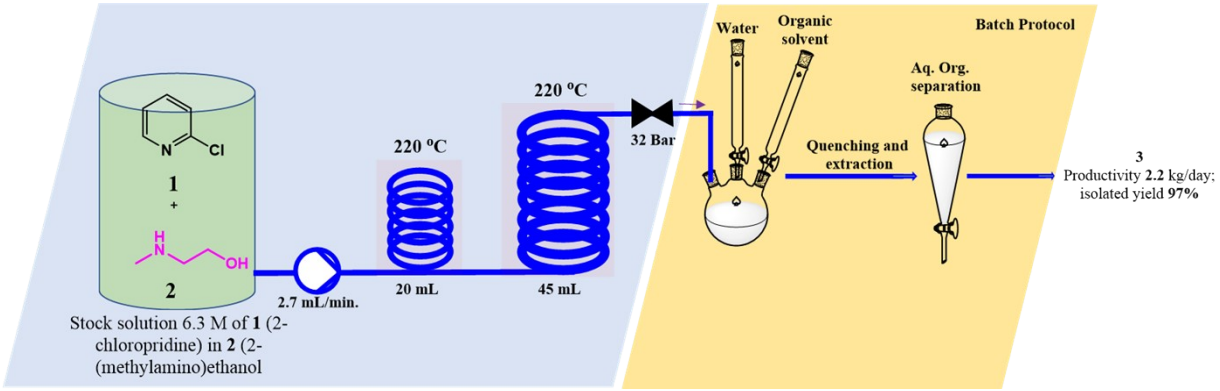


Figure S1. Schematic presentation of semi-continuous flow process to synthesize Rosiglitazone intermediate **3**.

3. Optimization of micro-separator platform for extraction and separation of Rosiglitazone intermediate 3.

Fabrication of a pilot-scale liquid-liquid separator: As illustrated in figure S2, laser ablation on PTFE film was employed to fabricate the proposed dual channel device. First of all, layers of 1 mm thick PTFE films were ablated by UV laser, to form 110 squares well (12 mm width × 12 mm length) and direction layer containing the rectangular 109 wells (6 mm width × 15 mm length). The 4-corners of each film were drilled for holes (1 mm dia.) to align the film patterns. After laser ablation, the films were cleaned by washing with acetone under ultrasonic and dried. Polytetrafluoroethylene (PTFE) membrane (whatmann, 0.45 μm pore, 47 mm dia.) sandwiched by two sheets of PTFE film with an identical dimension of microchannel were placed between Nylon frame holder, which were aligned each other by inserting metal bolt through the holes at the film corners. Finally, nylon frame holder was tightly pressed by screw to seal the device with no leak.

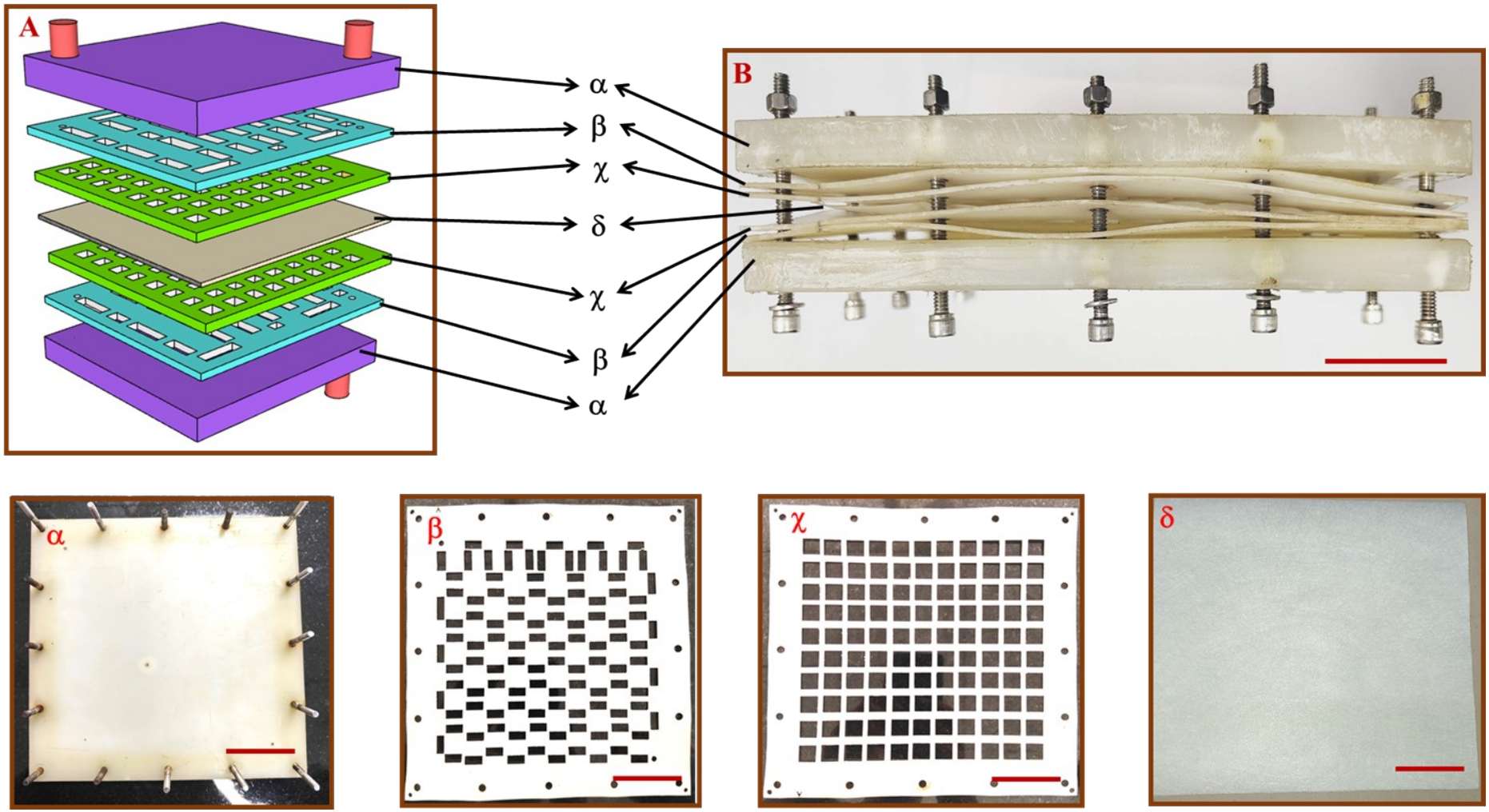


Figure S2. Schematic diagram of pilot scale liquid-liquid separator, (A) 3D model; (B) original photograph; (α) nylon fabric sheet (β) direction channel; (χ) square well PTFE channel; (δ) polypropylene coated PTFE membrane, bar represent the 5 cm.

Solvent Extraction optimization: The out-flowing crude solution of compound **3** from the combination of 20 mL SS-tubing reactor (1/16 inch OD tubing id 1 mm) and 45 mL SS-tubing reactor (1/8 inch OD tubing id 2 mm) (total reactor volume 65 mL) introduced to X-junction quenched by organic solvent and aqueous through the X-junction by using HPLC pumps. The outlet of X-junction connected to the PFA-tubing reactor (reactor volume 8 mL) then additional PTFE membrane-embedded phase separator was connected to the outlet of the PFA-tubing reactor as shown in (Figure S3). A serial process of droplet formation, extraction, and separation for purification of compound **3** was conducted in droplet microfluidics equipped with the PTFE membrane micro separator, as explained in a stepwise manner. Step 1: At first, the formation of alternating organic-aqueous droplets by introducing organic solvent and aqueous into the crude product mixture through X-junction. Secondly, extraction of reaction wastes into the aqueous stream by passing through a length of PFA-tubing during 0.3 min. Step 2: Finally, complete separation of the mixture of reactant and product containing organic phase by wetting and crossing through thin fluoropolymer membrane to the bottom of the separator, whereas the aq. waste containing the remaining compound **2** (which is miscible in water) did not wet the membrane and passed as the original stream (Table 2).

4. Procedure for the synthesis, extraction and separation of Rosiglitazone intermediate 3.

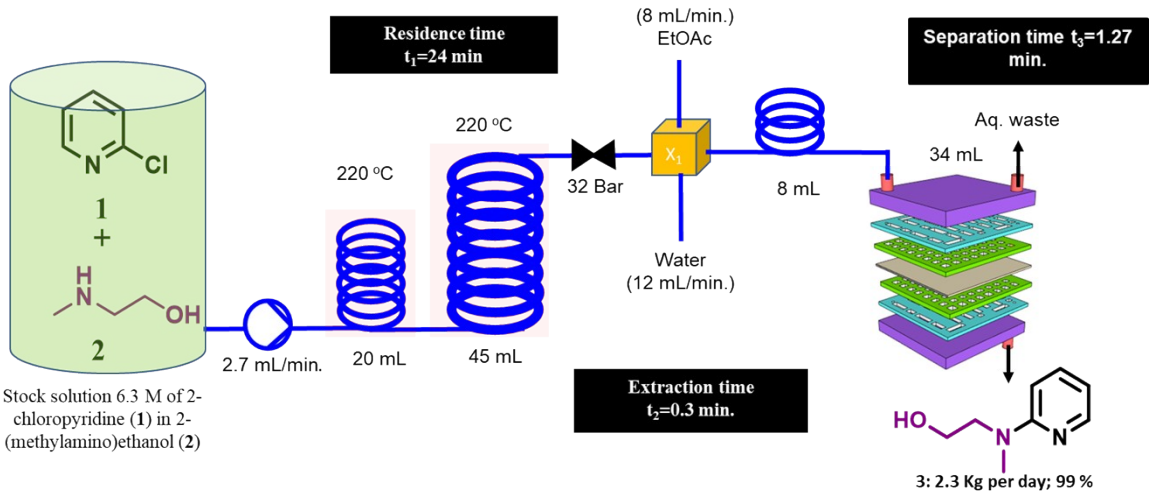
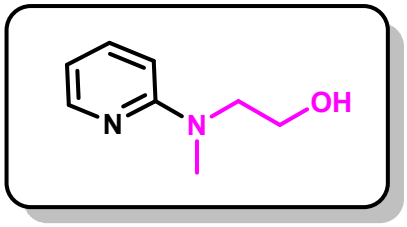


Figure S3. Schematic presentation of continuous flow for the synthesis, extraction and separation of Rosiglitazone intermediate **3**.

*Integrated continuous-flow Rosiglitazone synthesis of intermediate **3**, and downstream process*. A stock solution of compound **1** (2-chloropyridine) (6.3 M) in compound **2** (2-(methylamino)ethanol) and then passed through the combination of 20 mL SS-tubing reactor (1/16 inch OD tubing id 1 mm) and 45 mL SS-tubing reactor (1/8 inch OD tubing id 2 mm) (total reactor volume = 65 mL) with a flow rate of 2.7 mL/min. for the nucleophilic substitution reaction to occurs with the residence time 24 min., 220 °C temperature, 32 bar pressure (Figure S3). Next, the output of the crude reaction mixture was quenched with water and organic solvent with varied flow rate and then smoothly passed through Polytetrafluoroethylene (PTFE) tubing (id = 1000 µm, length = 10.4 m, vol. = 8 mL) for the extraction to occur. A residence time of 0.3 min., 25 °C temperature was found to be enough for the extraction of the compound **3** (Table 2, entry 4). After the successful completion of the extraction, next the organic-aqueous segment was separated by passing through our designed homemade micro separator (Figure S2). A residence time of 1.27 min., 25 °C temperature was found to be enough for the complete separation of aqueous and organic layer (Table 2, Entry 4). The extracted waste aqueous layer was further extracted with EtOAc and analysed by GC-MS, which showed



no product and was also confirmed by the absence of the corresponding peaks in the crude NMR analysis (^{1}H and ^{13}C NMR spectra). The reaction mixture solvent was removed under the vacuum and give the intermediate 3 The extracted mixture was purified by silica gel column chromatography (80: 20; Hexane: EtOAc) to provide yellow oily liquid compound **3** of yield 99%. The spectra data matched with values reported in the literature.[3] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 – 8.04 (m, 1H), 7.47 – 7.45 (m, 1H), 6.59 – 6.56 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 5.38 (s, 1H) 3.85 – 3.83 (t, *J* = 8.6 Hz, 2H), 3.72 – 3.69 (t, *J* = 4.0 Hz, 2H), 3.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.38, 147.09, 137.84, 112.33, 106.37, 63.13, 54.46, 37.99. **IR (ν_{max}):** 3438, 3372 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_8H_{12}N_2O$** $(M+H)^+$ 153.1028, Found 153.1023.

Space-time yield (STY) for the formation of compound 3.

$$\text{Space-time yield (STY)} = \frac{Product\ mol}{reactor\ vol.\ X\ operation\ time}$$

Reactor vol. = 65 mL

Molecular weight of compound 3 = 152 g/mol

Productivity/day = 2.3 kg/day = 2300 g/day

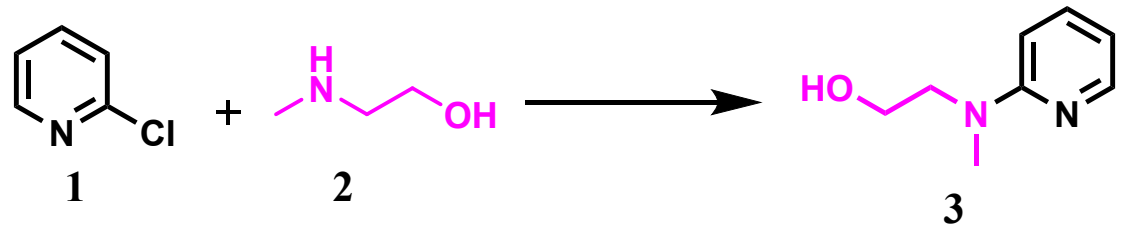
$$\text{Product mol} = \frac{2300}{152}$$

$$= 15.13 \text{ mol}$$

$$\text{Space-time yield (STY)} = \frac{15.13\ mol}{65\ mL\ X\ 1\ day}$$

$$= 0.233 \text{ mol mL}^{-1} \text{ day}^{-1}$$

Table S1. Comparative study for synthesis of Rosiglitazone intermediate **3.**



Entry	Process	Comp 1 (eq.)	Comp 2 (eq.)	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	1	6	720	165	99	[3]
2	batch	1	1	780	120	90	[4]
3	batch	1	12.5	900	120	63	[5]
4	batch	1	3	480	150	92	[6]
5	batch	1.5	1	900	160	66	[7]
6	**flow**	**1**	**2**	**24**	**220**	**99**	**this study**

5. Optimization for the continuous flow production of Rosiglitazone intermediate 5.

Nucleophilic substitution reaction (N-platform): A stock solution of compound **3** in DMF was charged in one syringe. A stock solution of compound **4** in DMF was charged in another syringe. The two solutions were introduced into a T-mixer with variable flow rates to maintain the stoichiometric ratio and then passed through to a packed bead KOH cartridge (id = 7 mm, length = 150 mm, vol. = 6 mL) with varied residence time, temperature, pressure, etc. for the reaction to occur. Optimization conditions were varied depending on the nature of the reagent, residence time, temperature, pressure, etc. (Table 3).

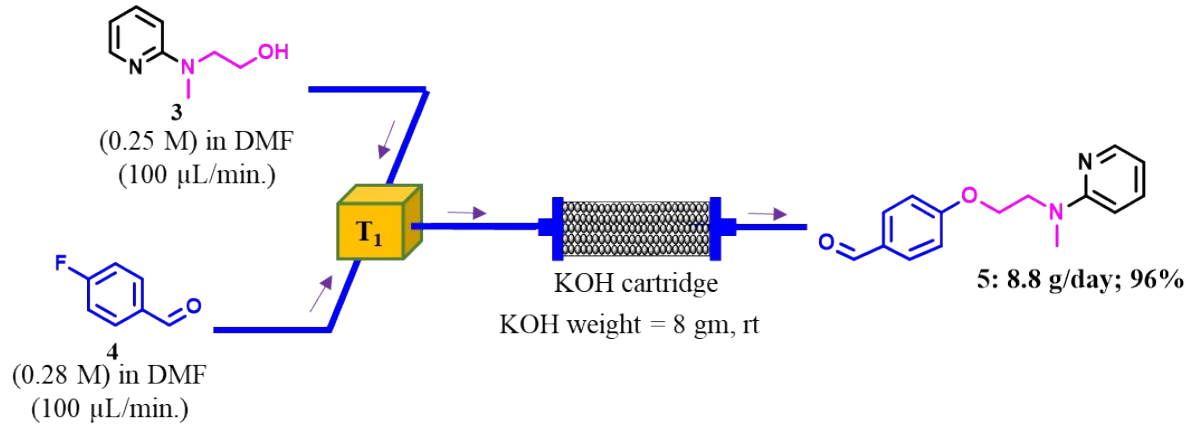


Figure S4. Schematic presentation of continuous flow process to synthesize Rosiglitazone intermediate **5**.

Packed bead KOH cartridge long term efficiency: The continuous intermediate **5** synthesis setup as aforementioned in figure S4. Stock solution of compound **3** (0.25 M in DMF) and stock solution of compound **4** (0.28 M in DMF) were charged in two separate syringes. Stock solutions of Compound **3** and compound **4** was introduced into a T-mixer with same flow rate of 100 µL/min. using two separate pumps. The outlet of the T-mixer was connected to a packed bead KOH cartridge (id = 7 mm, length = 150 mm, vol. = 6 mL). The out-flowing product mixture of **5** from pack bead KOH cartridge was analysed by GC-MS and data has been plotted on figure 2.

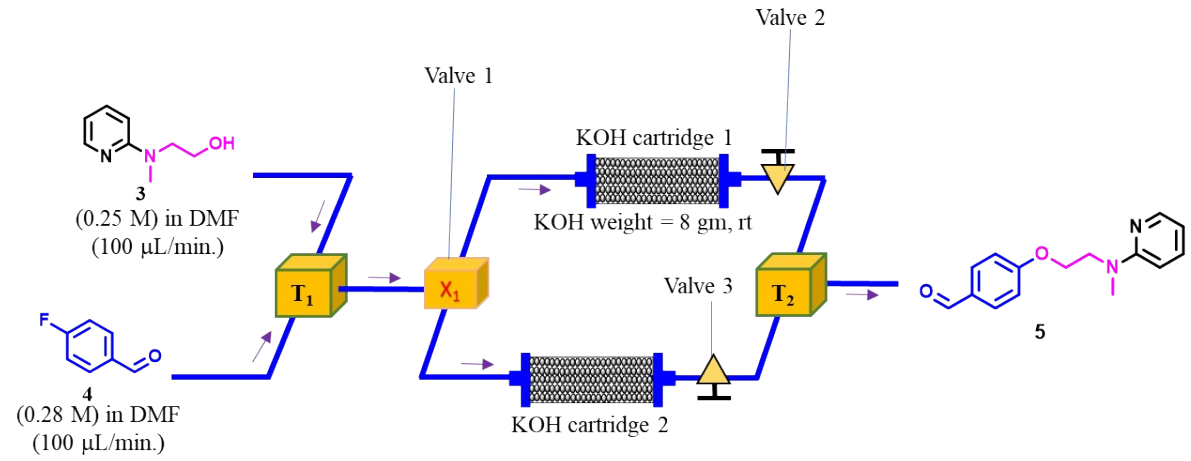
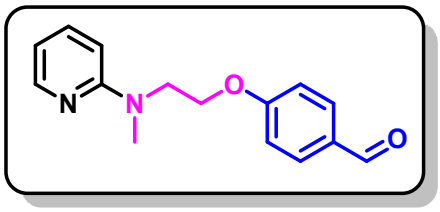


Figure S5. Continuous flow integrated system for synthesis of Rosiglitazone intermediate **5**.

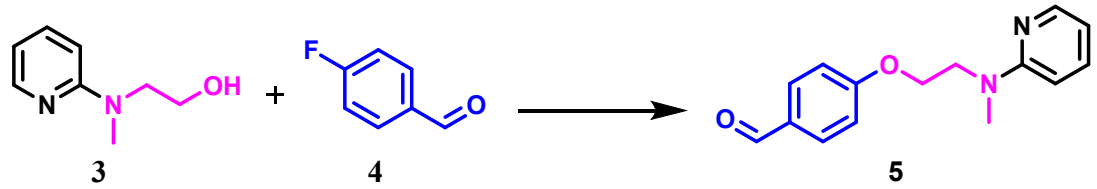


*Optimized condition for the continuous flow synthesis of Rosiglitazone intermediate **5**.*

The continuous intermediate **5** synthesis setup as aforementioned in figure S5. Stock solution of compound **3** (0.25 M in DMF) and stock solution of compound **4** (0.28 M in DMF) in same flow of flow rate 100 µLmin^{-1} were introduced into a T-mixer through a PTFE tubing (id = 1 mm, length = 20 cm). The outlet of the T-mixer was connected to valve 1. The directional valve 1 has two outlets and each outlet was S26 connected with pack bead KOH cartridge (id = 7 mm, length 150 mm, vol = 6 mL). After completion of the reaction, the packed bead KOH cartridge was connected by another PTFE tubing (id = 1 mm, length = 15 cm) to directional valve 2. One KOH cartridge efficiently working for 88 hours later on feed solution direction changed by valve to the reserved second catalytic cartridge and mean while time cartridge was refilled and again continued. The out-flowing product mixture **5** from the packed KOH cartridges were analysed by LC-MS and data has been plotted on figure 3. The collected mixture was purified by silica gel column chromatography (85: 15; Hexane: EtOAc) to provide a yellow oily liquid **5** of Yield 92%. Analytical data are well matched with reported literature.[3] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.86 (s, 1H), 8.16 – 8.15 (m, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.48 – 7.44 (m,

1H), 7.00 (d, J = 8.7 Hz, 2H), 6.58 – 6.55 (m, 1H), 6.51 (d, J = 8.6 Hz, 1H), 4.28 (t, J = 5.7 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 3.14 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.92, 164.06, 158.32, 148.01, 137.49, 132.10, 130.06, 114.92, 112.08, 105.83, 66.85, 49.42, 38.04. **IR (ν_{max}):** 1690 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{15}H_{16}N_2O_2$** $(M+H)^+$ 257.1288, Found 257.1283.

Table S2. Comparative study for synthesis of Rosiglitazone intermediate **5**.



3 **4** **5**

Entry	Process	Base	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	NaH	1440	50	50	[3]
2	batch	NaH	1080	25	48	[5]
3	batch	K-tBuO	overnight	80	47	[8]
4	batch	NaH	1080	80	44	[7]
5	**flow**	**KOH**	**10**	**25**	**96**	**this study**

6. Optimization for the continuous flow production of Rosiglitazone intermediate 8.

*Knoevenagel condensation reaction (K-platform)***.** A stock solution of compound **5** in DMF was charged in one syringe. A stock solution molar ratio of compound **6:**compound **7**:**MeOH** was charged in another syringe. The two solutions were introduced into a T-mixer with variable flow rates to maintain the stoichiometric ratio and then passed through the SS-tubing reactor (reactor volume 8 mL) with varied residence time, temperature, pressure, etc. for the reaction to occur. Optimization conditions were varied depending on the nature of the reagent, residence time, temperature, pressure, etc. (Table 4).

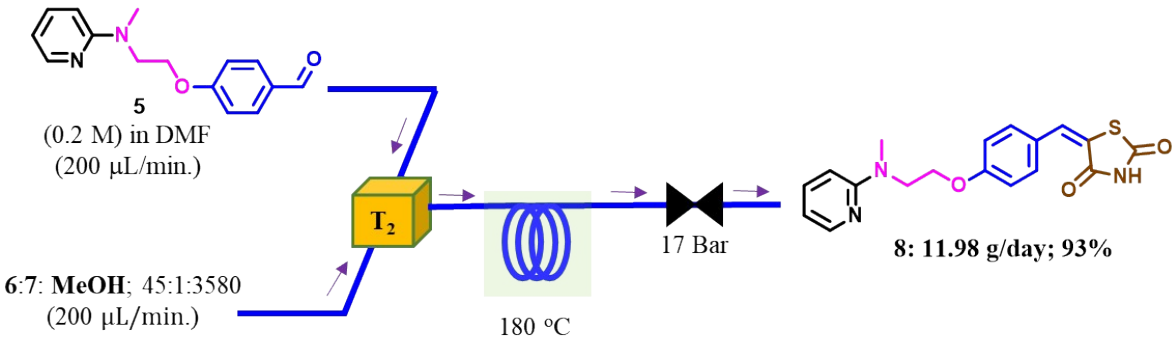
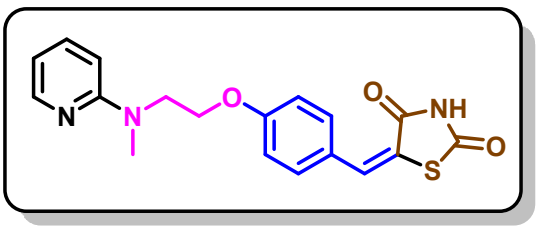


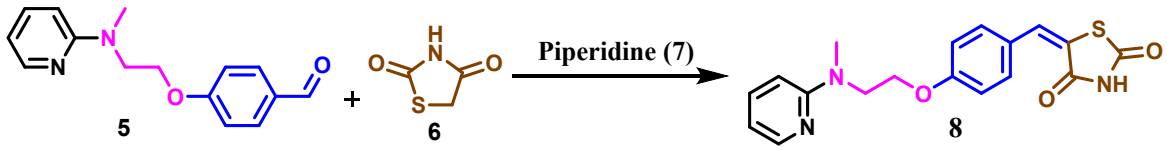
Figure S6. Schematic presentation of continuous flow process to synthesize Rosiglitazone intermediate **8.**



*Optimized condition for continuous production of Rosiglitazone intermediate **8***. A stock solution of compound **5** (0.25M in DMF) and stock solution molar ratio of compound **6**:compound **7**:**MeOH** (45:1:3580) were introduced into capillary microreactor with a T-mixer using two separate pumps (Figure S6). The flow rate of stock solution of compound **5** was kept at same the rate of stock solution molar ratio of compound **6**: compound **7** : MeOH, following the stoichiometry of reagent and substrates. A residence time of 20 min., temperature180 °C, and 17 bar pressure was found enough for the synthesis of compound **8** (Table 4, Entry 5). The processed mixture left the flow reactor as a one-phase DMF/MeOH solution. The solvent from the organic phase

was removed under reduced pressure, and the regular extraction and purification process provided compound **8** in 93% yield and **melting point:** 192-194 °C. The spectra data matched with values reported in the literature.[3] **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.09 – 8.07 (m, 1H), 7.73 (s, 1H), 7.54 – 7.48 (m, 3H), 7.12 – 7.08 (m, 2H), 6.65 (d, J = 8.6 Hz, 1H), 6.58 – 6.55 (m, 1H), 4.22 (t, J = 5.9 Hz, 2H), 3.92 (t, J = 5.9 Hz, 2H), 3.07 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 168.06, 167.66, 160.16, 158.00, 147.54, 137.37, 132.09, 131.65, 125.60, 120.52, 115.36, 111.61, 105.78, 65.81, 48.33, 37.07. **IR (ν_{max}):** 1692 cm^{-1}; **HRMS (ESI):** *m/z* calcd for **$C_{18}H_{17}N_3O_3S$** $(M+H)^+$ 356.1074, Found 356.1069.

Table S3. Comparative study for synthesis of Rosiglitazone intermediate **8**.



Entry	Process	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	360	110	80	3
2	batch	480	110	80	9
3	batch	1440	88	86	1
4	batch	240	110	64	10
5	**flow**	**20**	**180**	**93**	**this study**

7. Optimization for the continuous flow production of Rosiglitazone intermediate 9.

*Hydrogenation reaction condition (H-platform)***.** A stock solution of compound **8** was charged in a syringe and passed through the H-Cube reactor (reactor volume = 1 mL) for reduction reaction with variable flow rates, residence time, temperature, pressure, etc. for the reaction to occur. Optimization conditions were varied depending on the nature of the reagent, retention time, temperature, pressure, etc. (Table 5).

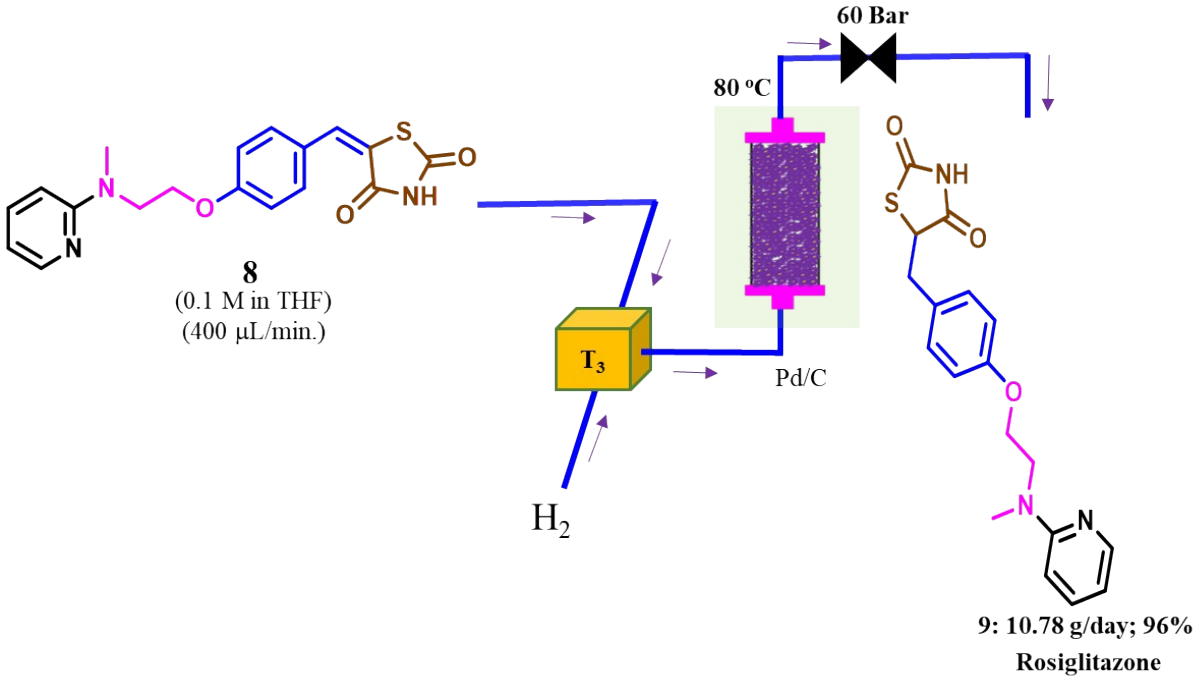
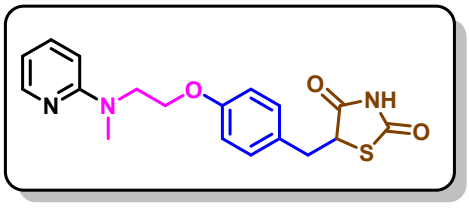


Figure S7. Schematic presentation of continuous flow process to synthesize Rosiglitazone intermediate **9**.

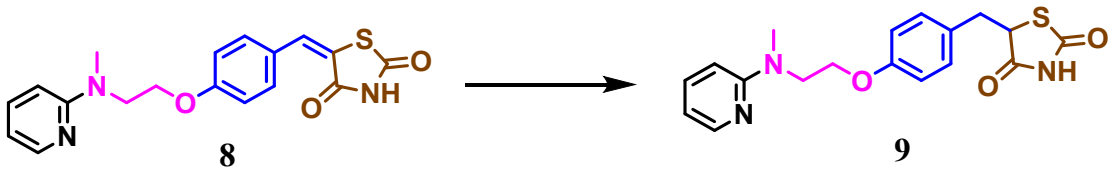
Optimized condition for continuous production of Rosiglitazone intermediate **9**.



A stock solution of compound **8** (0.1 M in THF) were introduced into H-Cube reactor using a pump (Figure S7). A residence time of 2.5 min., temperature 80 °C, and 60 bar pressure was found enough for the synthesis of compound **9** (Table 5, Entry 4). The solvent from the organic phase was removed under reduced pressure, and the regular extraction and purification process provided an off-white

solid compound **9** of yield 96% and **melting point**:152-154 °C. The spectra data matched with values reported in the literature.[3] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 5.0 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.57 – 6.54 (m, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 4.49 – 4.46 (m, 1H), 4.12 (t, *J* = 8.0 Hz, 2H), 3.96 (t, *J* = 8.0 Hz, 2H), 3.41 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.14 – 3.07 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.26, 170.49, 158.47, 158.34, 147.82, 137.54, 130.50, 127.75, 114.87, 111.90, 106.00, 66.41, 53.83, 49.70, 38.03, 37.85 **(ν_{max}):** 1697 cm^{-1}; **HRMS (ESI):** *m/z* calcd for **$C_{18}H_{19}N_3O_3S$** $(M+H)^+$ 358.1218, found 358.1213.

Table S4: Comparative study for synthesis of Rosiglitazone **9**



8 **9**

Entry	Process	Catalyst	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	$NaBH_4$, NaOH, $CoCl_2$, DMG	1440	25	91	3
2	batch	Mg, Iodine	180	Reflux	80	4
3	batch	Mg, Iodine	240	25	62	5
4	batch	Pd/C, H_2	1440	25	100	11
5	flow	Pd/C, H_2	2.5	80	96	this study

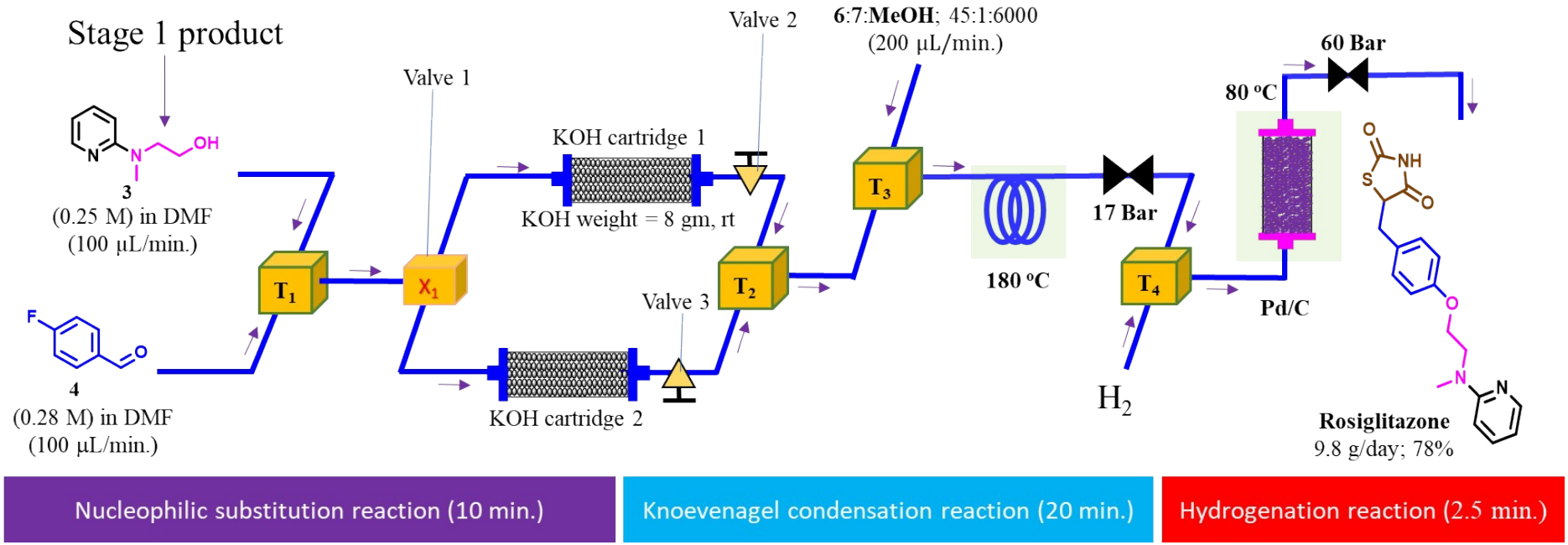
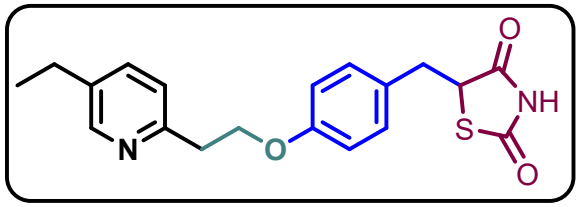


Figure S8. Schematic presentation of the Rosiglitazone synthesis through the NKH-platform.

For synthesizing Rosiglitazone in integrated continuous flow (NKH-platform), we passed the stock solutions of compound **3** (0.25 M in DMF) and compound **4** solution (0.28 M in DMF) at the same flow rate of 100 µL/min. and mixed with T-junction (T_1) (Figure S8). The outlet of the T-junction is connected to valve 1, which has two outlets and both outlets connected to the two bead packed KOH cartridges. When we pass the reaction mixture through valve 1 and the direction of valve 1 is towards the bead packed KOH cartridge 1 and closed valve 3, the reaction mixture passes through valve 1 in the direction of the bead-packed KOH cartridge 2. Out-flowing reaction mixture from KOH catridge was further connected with another T-junction (T_3). Another side stock solution of **6**:**7**:**MeOH** (45:1:6000) with a flow rate 200 µL/min. was introduced. This mixed reaction mixture was connected to 8 mL PTFE-tubing reactor for further reaction at 180 ^{o}C and 17 bar pressure. The crude reaction mixture of compound **8** outlet is connected to the H-cube HPLC pump for hydrogenation reaction using a 10% Pd/C catalyst at a flow rate of 400 µL/min., temperature of 80 ^{o}C and pressure of 60 bar, resulting in final target compound **9** (Rosiglitazone) with an yield of 78%; within of residance time 32.5 min. and productivity 9.8 g/day (Figure S8).

8. NKH-platform for on-demand Rosiglitazone and Pioglitazone synthesis:



As shown in Figure 5, we have interconnected to another valve to interchange the reagent **3** with the reagent **10** and rest of the part we kept same like above mentioned in rosiglitazone synthesis. In this case we obtained the 80% of the product yield by using the same NKH-platform; productivity: 10.1 g/day (Figure 5) and **melting point:** 182-184 ^{o}C. The spectra data matched with values reported in the literature.[12] **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.99 (s, 1H), 8.36 (d, *J* = 1.9 Hz, 1H), 7.56 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.84 (dd, *J* = 9.1, 4.3 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 3.22 (dd, *J* = 42.3, 4.5 Hz, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 3.03 (dd, *J* = 14.2, 9.1 Hz, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 175.93, 171.82, 157.48, 155.43, 148.54, 136.65, 135.68, 130.32, 128.65, 123.01, 114.32, 66.69, 53.10, 36.77, 36.31, 24.95, 15.40. **IR (ν_{max}):** 3121, 2940, 2770, 1754, 1704 cm^{-1}. **HRMS (ESI):** m/z calcd for **$C_{19}H_{20}N_2O_3S$** $(M+H)^+$ 357.1270, Found 357.1264.

9. Spectra

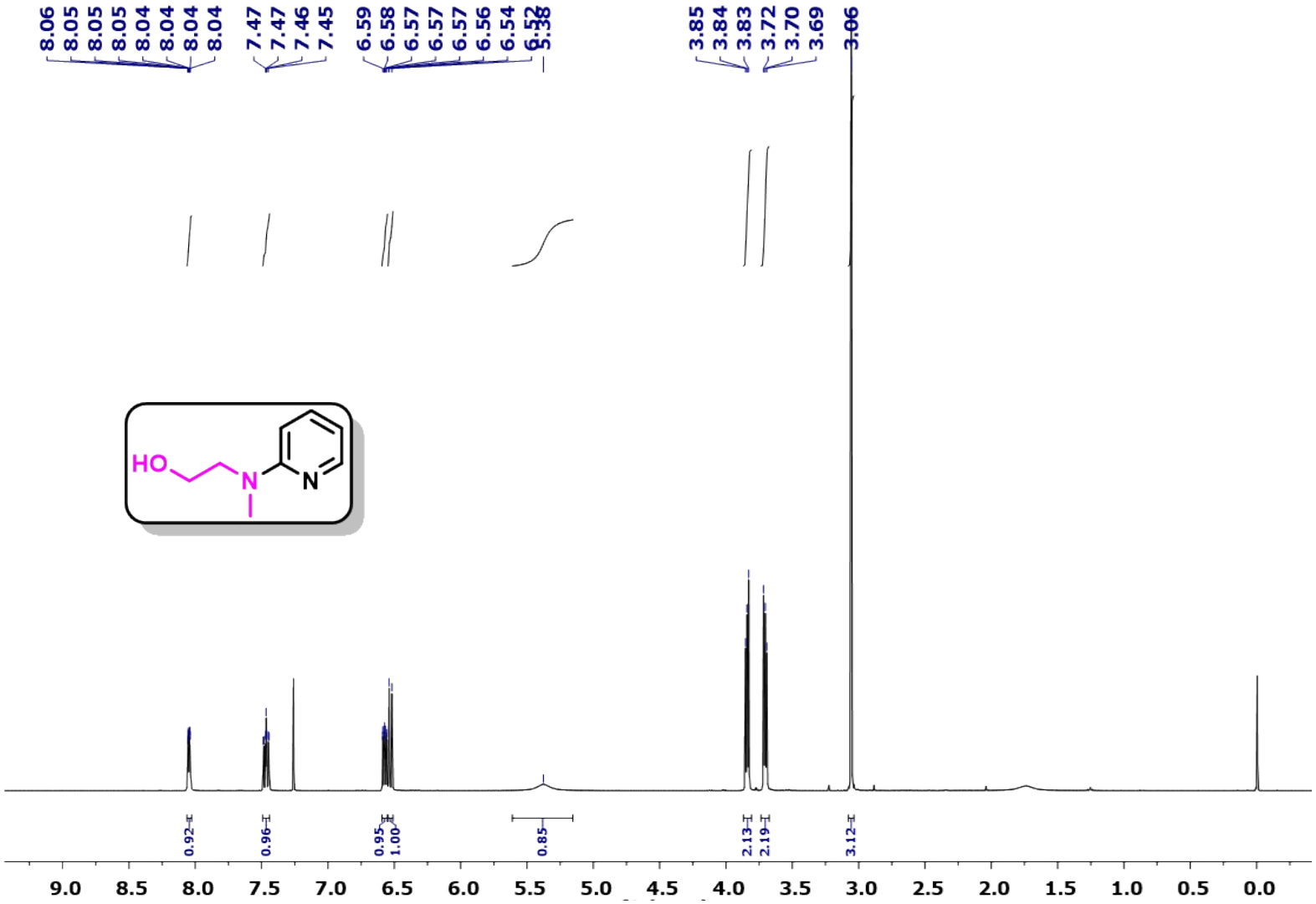


Figure S9. ^{1}H NMR spectra of 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (**3**) in $CDCl_3$ solvent.

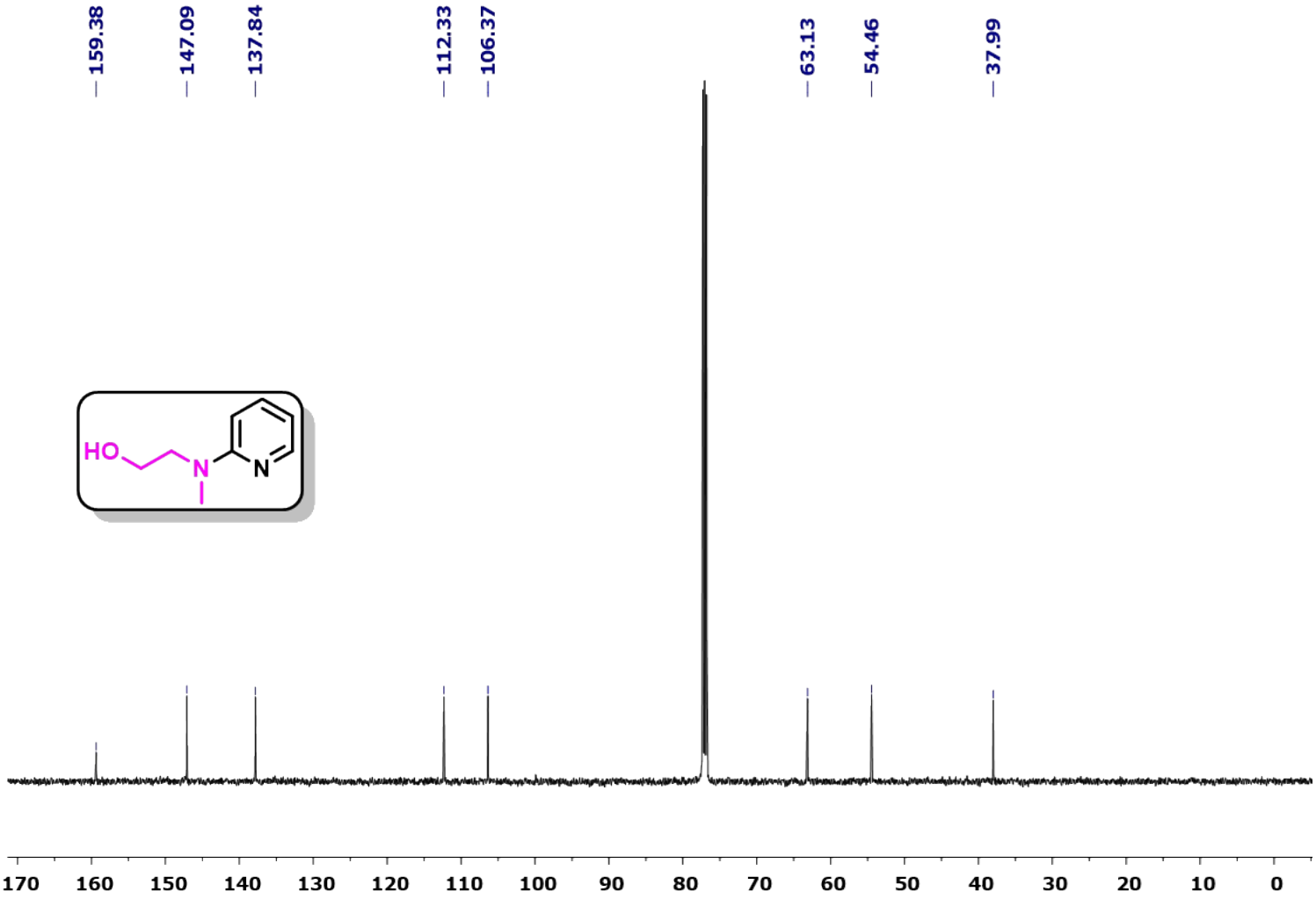


Figure S10. ^{13}C NMR spectra of 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (**3**) in $CDCl_3$ solvent.

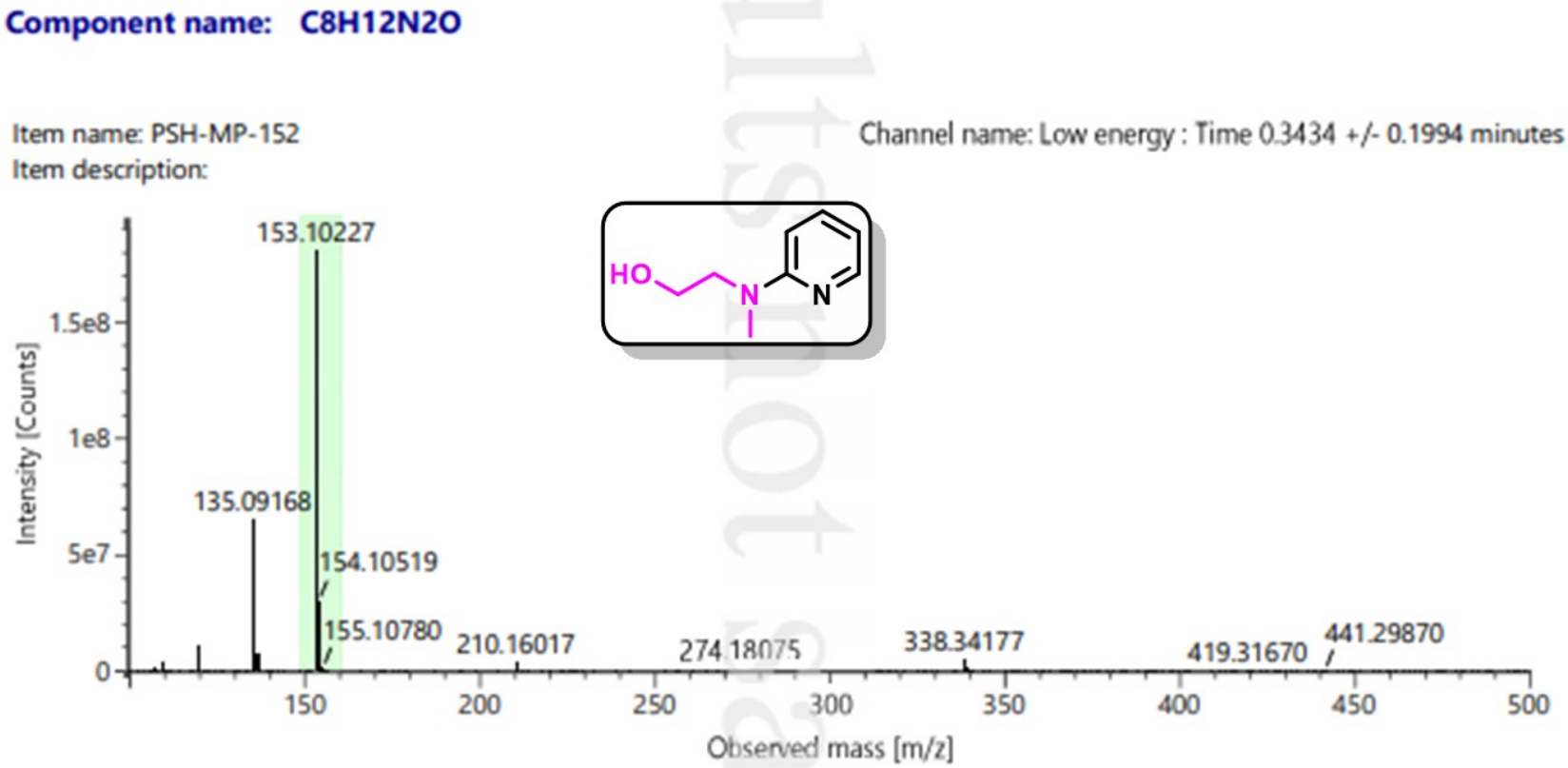


Figure S11. HRMS spectra of 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (**3**).

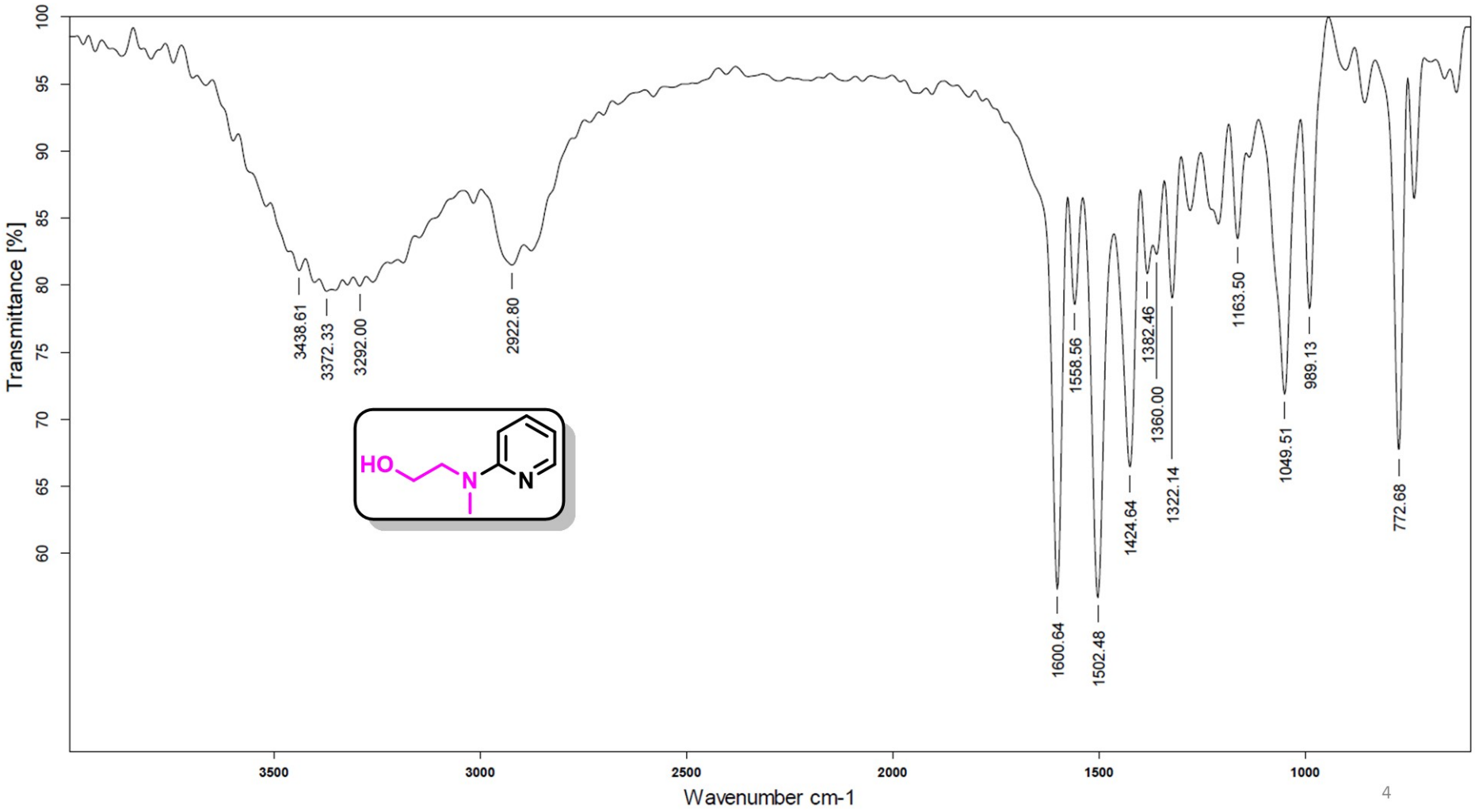


Figure S12. IR spectra of 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (**3**).

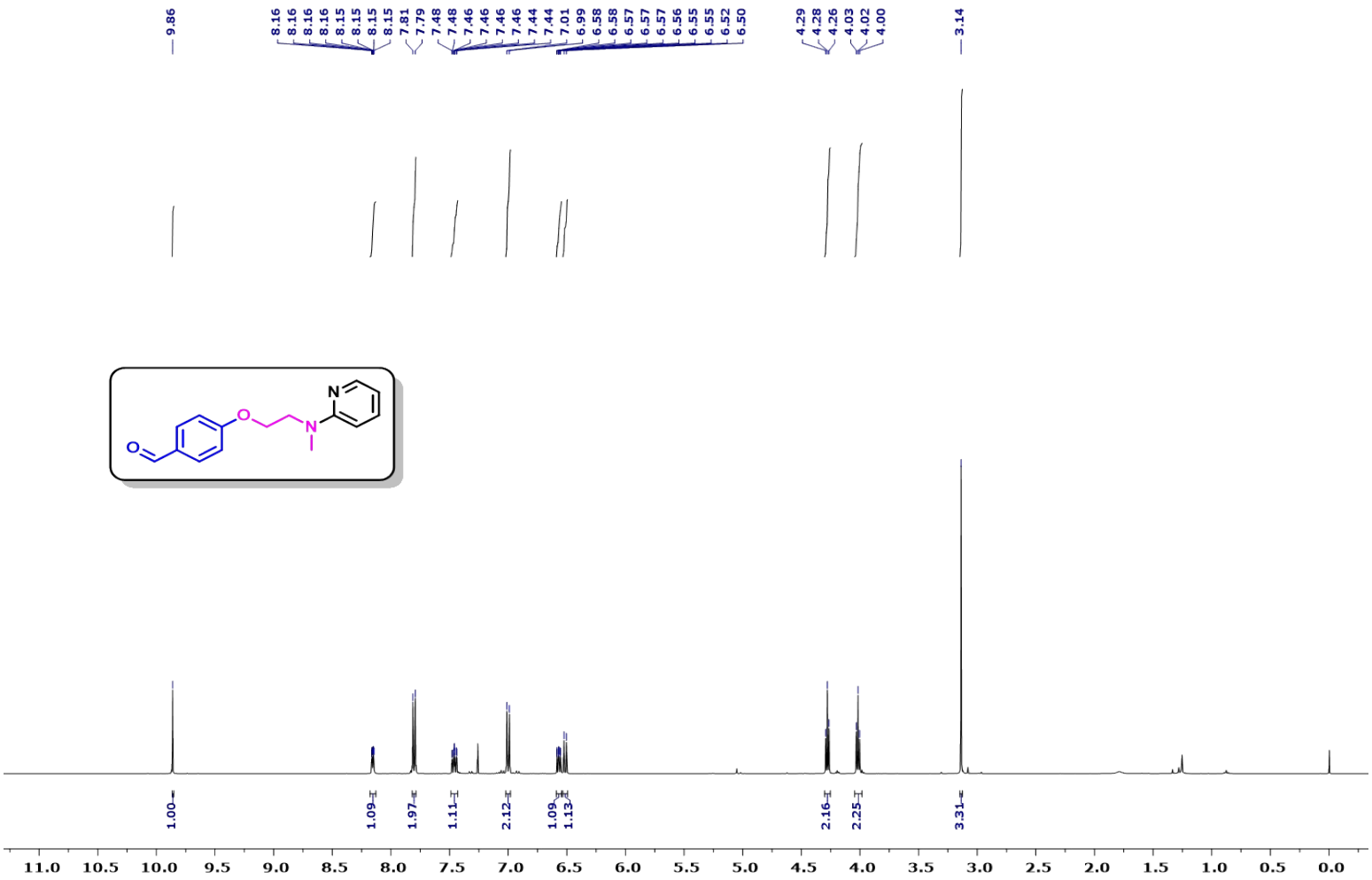


Figure S13. ^{1}H NMR spectra of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde (**5**) in $CDCl_3$ solvent.

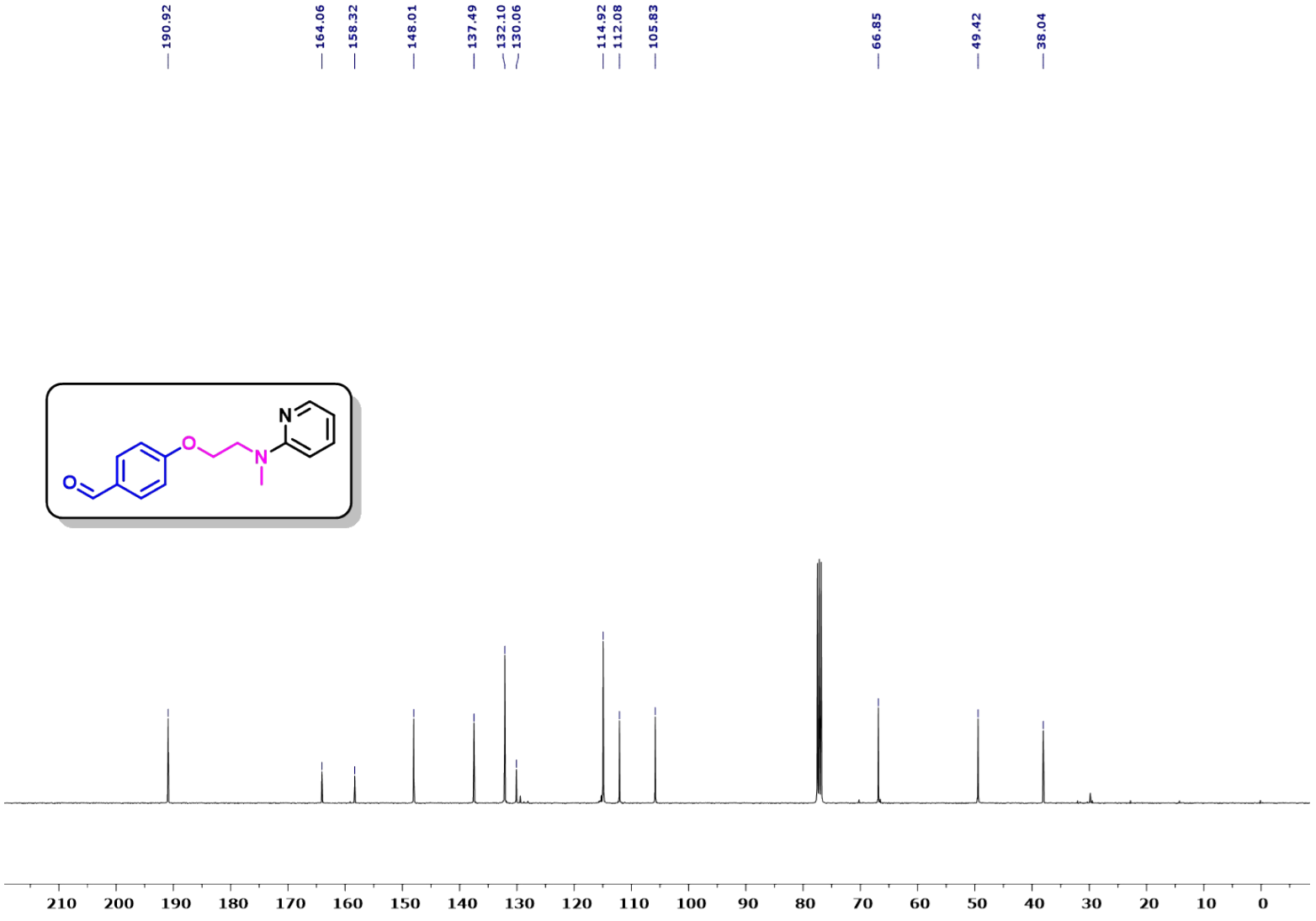


Figure S14. ^{13}C NMR spectra of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde (**5**) in $CDCl_3$ solvent.

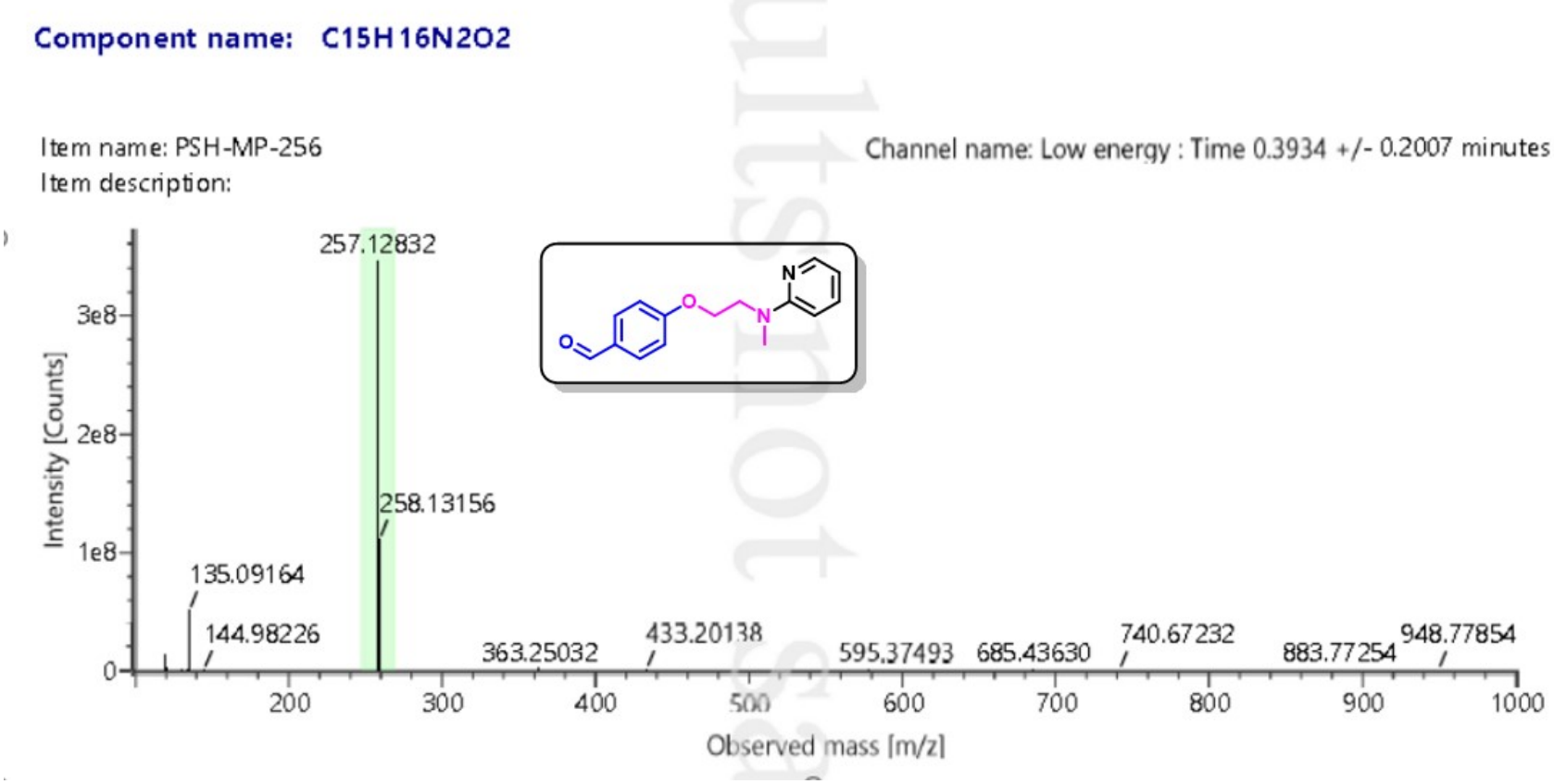


Figure S15. HRMS spectra of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde (**5**).

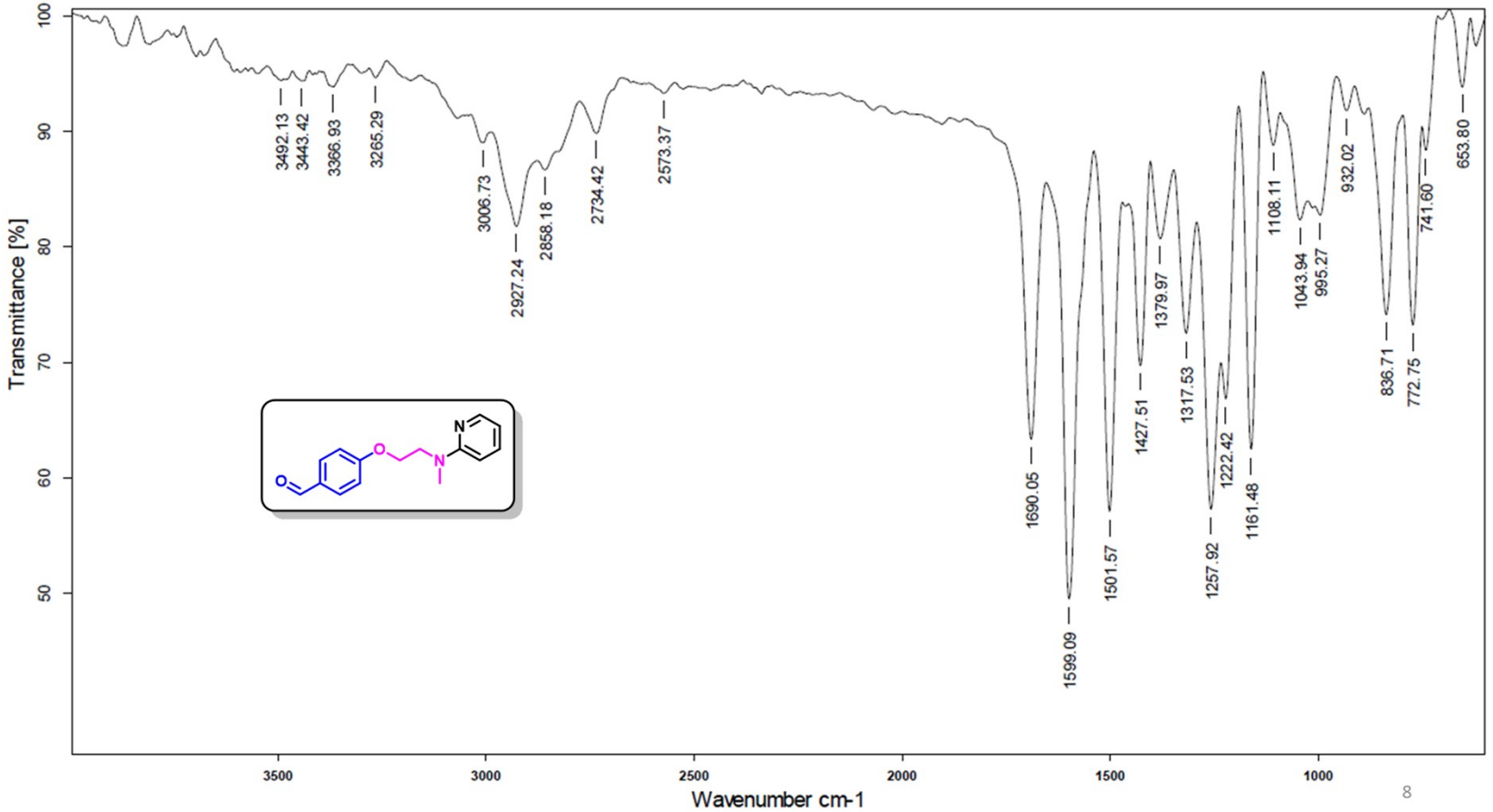


Figure S16. IR spectra of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde (**5**).

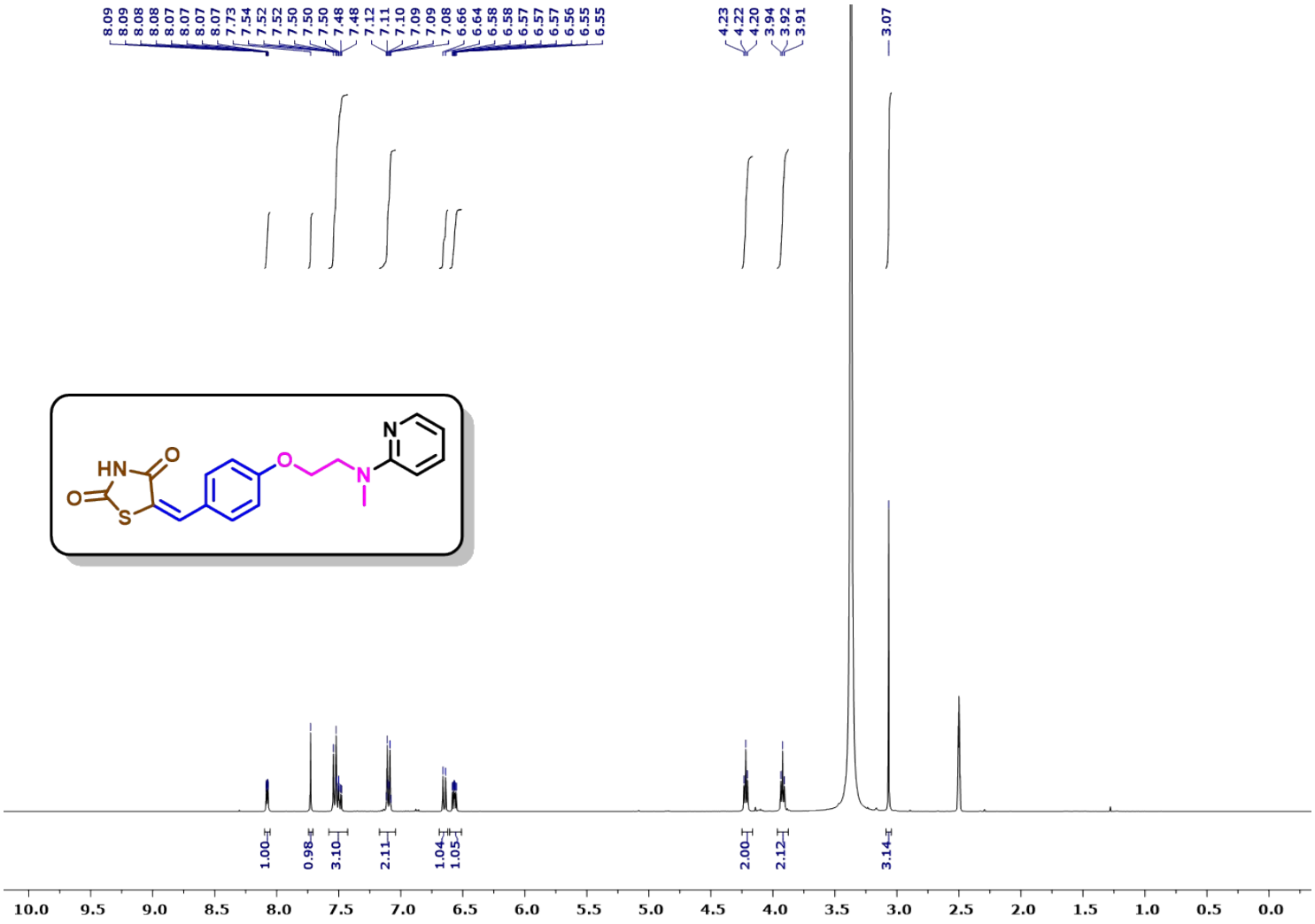


Figure S17. [1]H NMR spectra of (Z)-5-(4-(2-(methyl(pyridine-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (**8**) in DMSO-d_6 solvent.

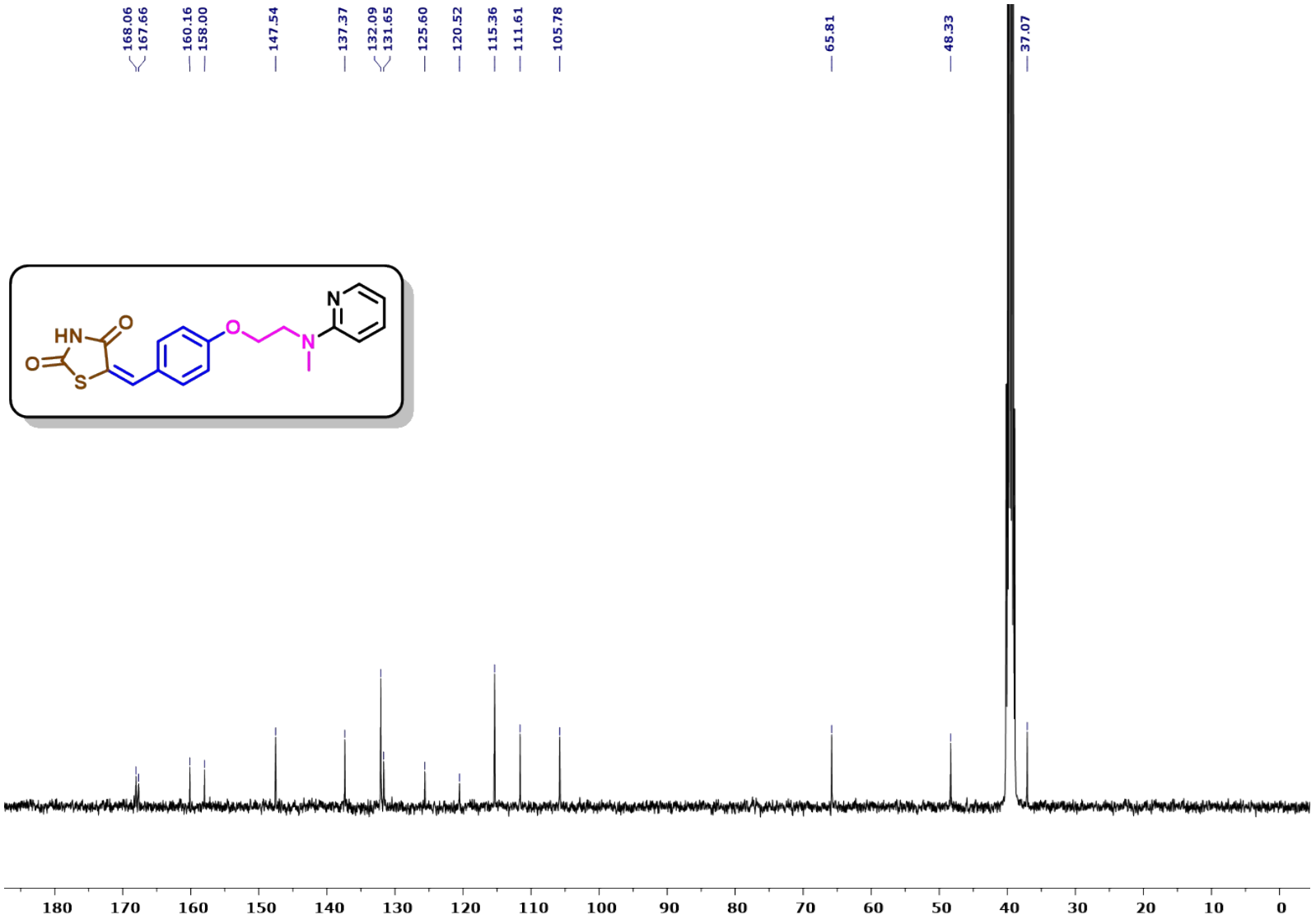


Figure S18. ^{13}C NMR spectra of (Z)-5-(4-(2-(methyl(pyridine-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (**8**) in DMSO-d_6 solvent.

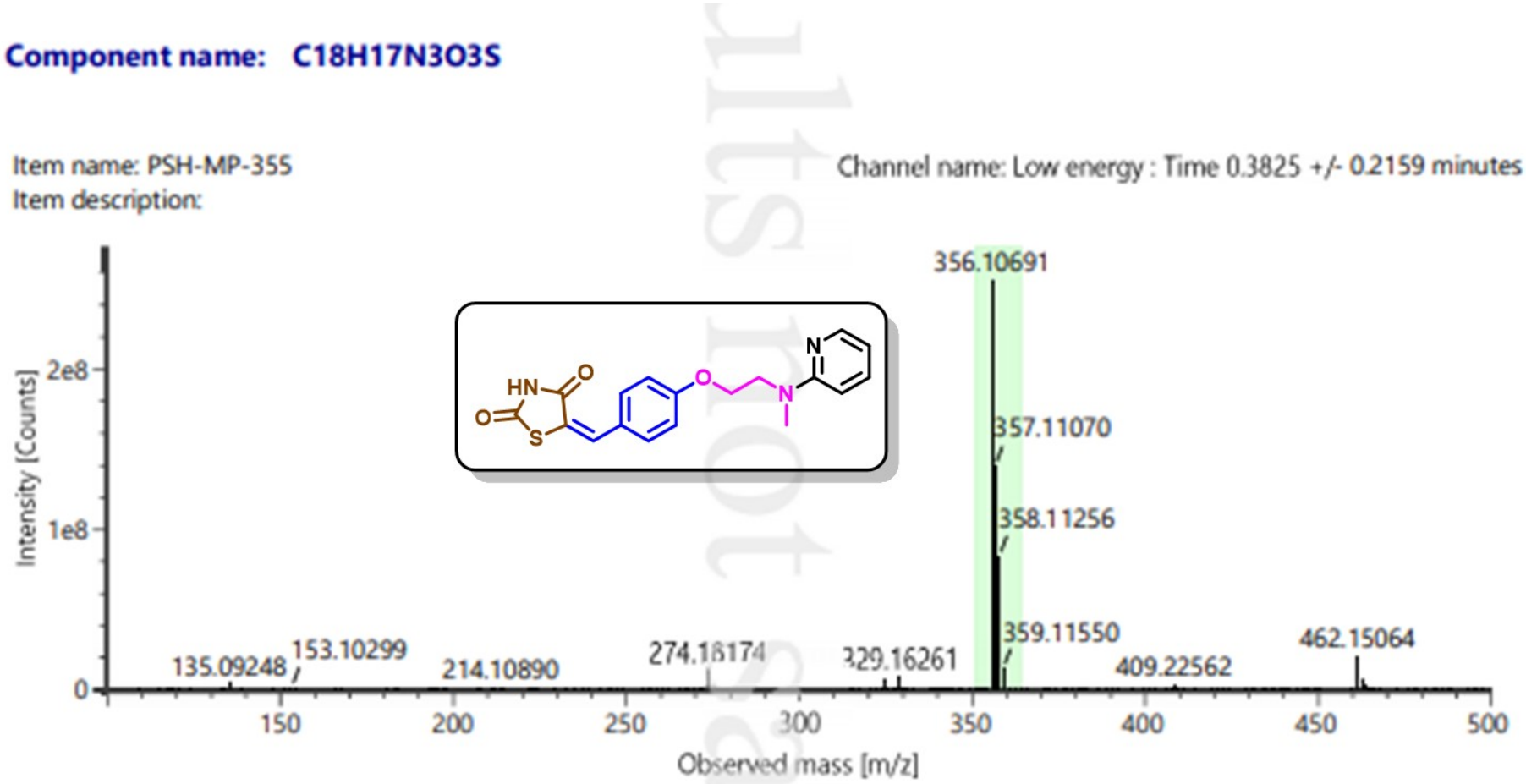


Figure S19. HRMS spectra of (Z)-5-(4-(2-(methyl(pyridine-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (**8**).

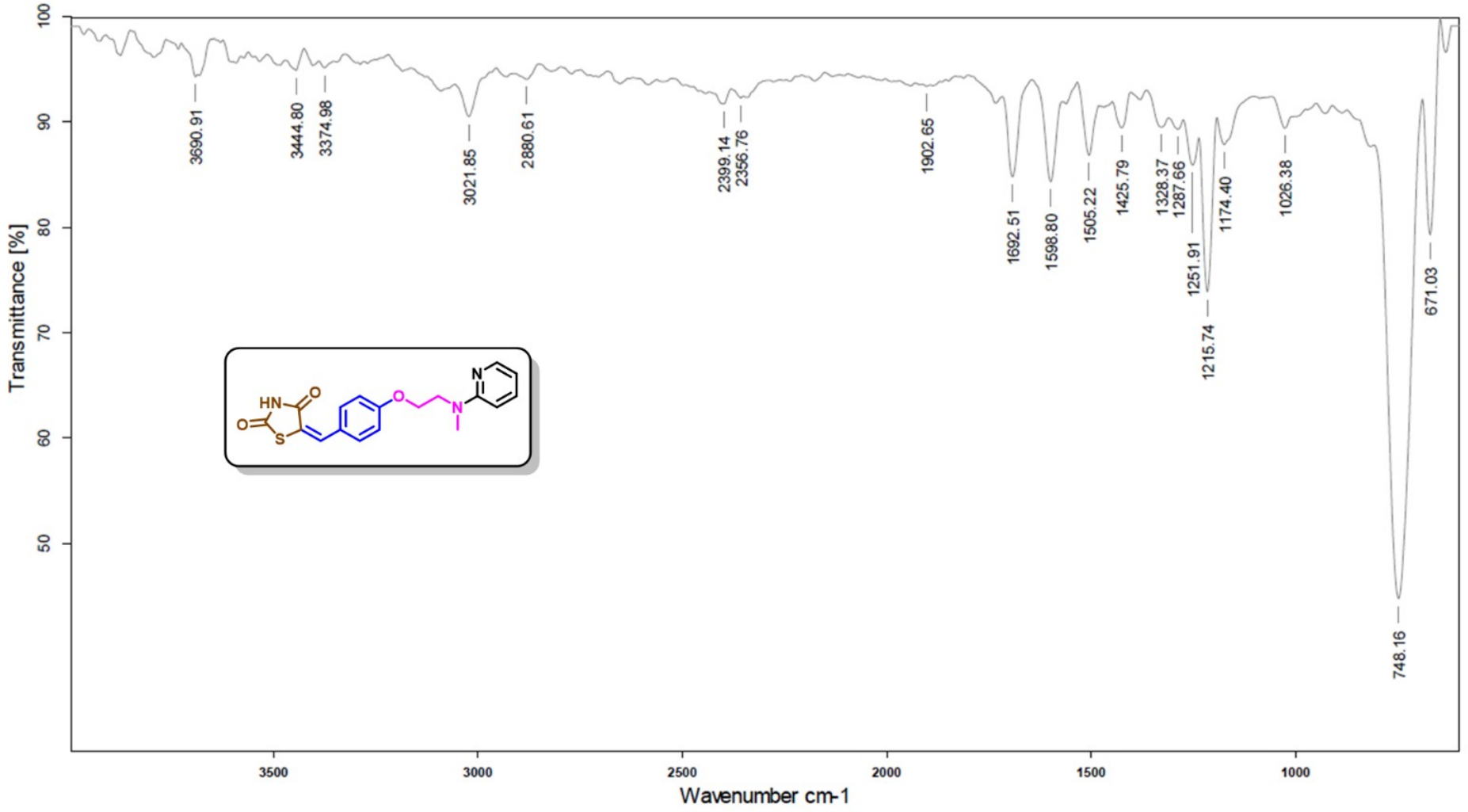


Figure S20. IR spectra of (Z)-5-(4-(2-(methyl(pyridine-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (**8**).

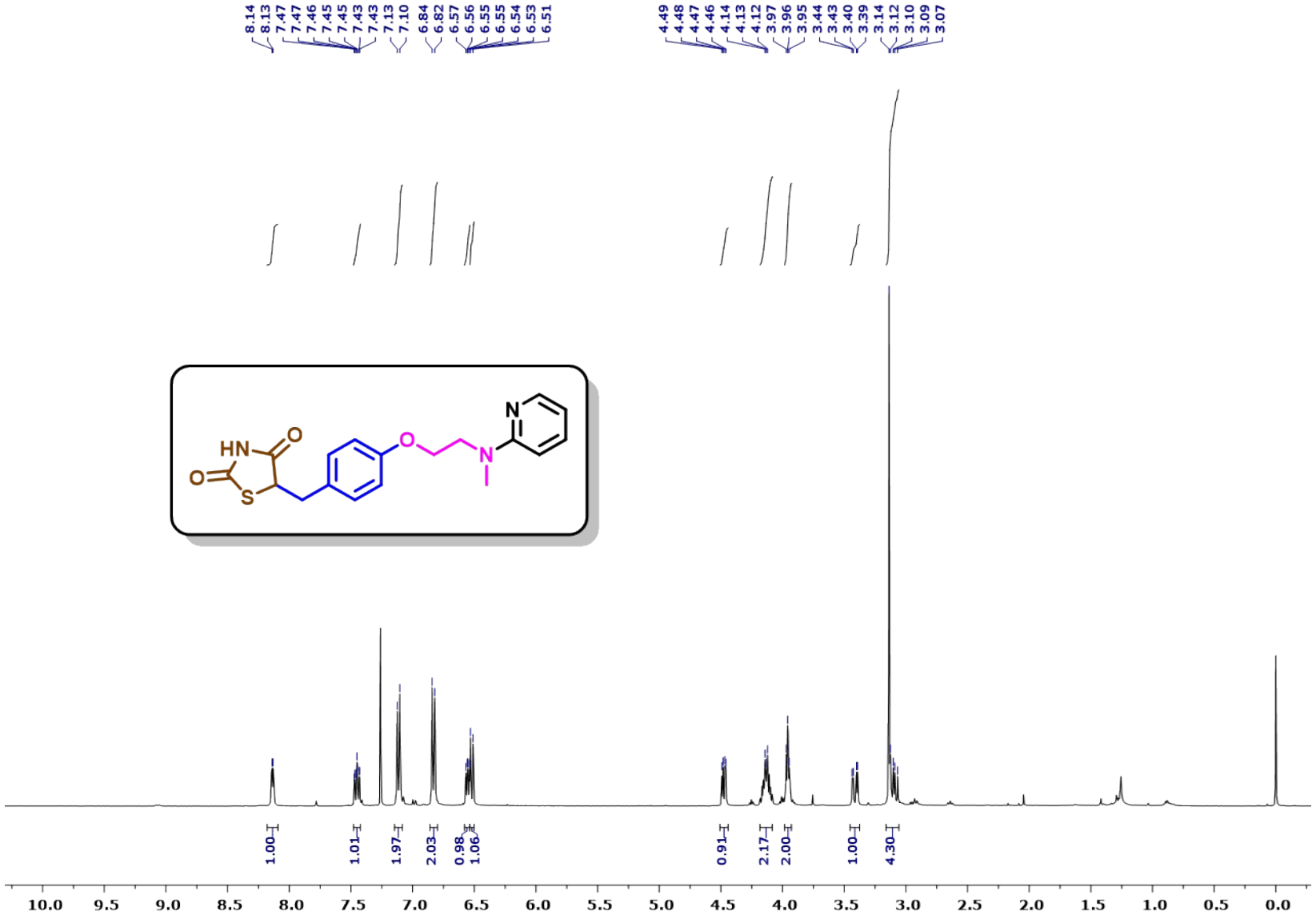


Figure S21. ^{1}H NMR spectra of Rosiglitazone (**9**) in $CDCl_3$ solvent.

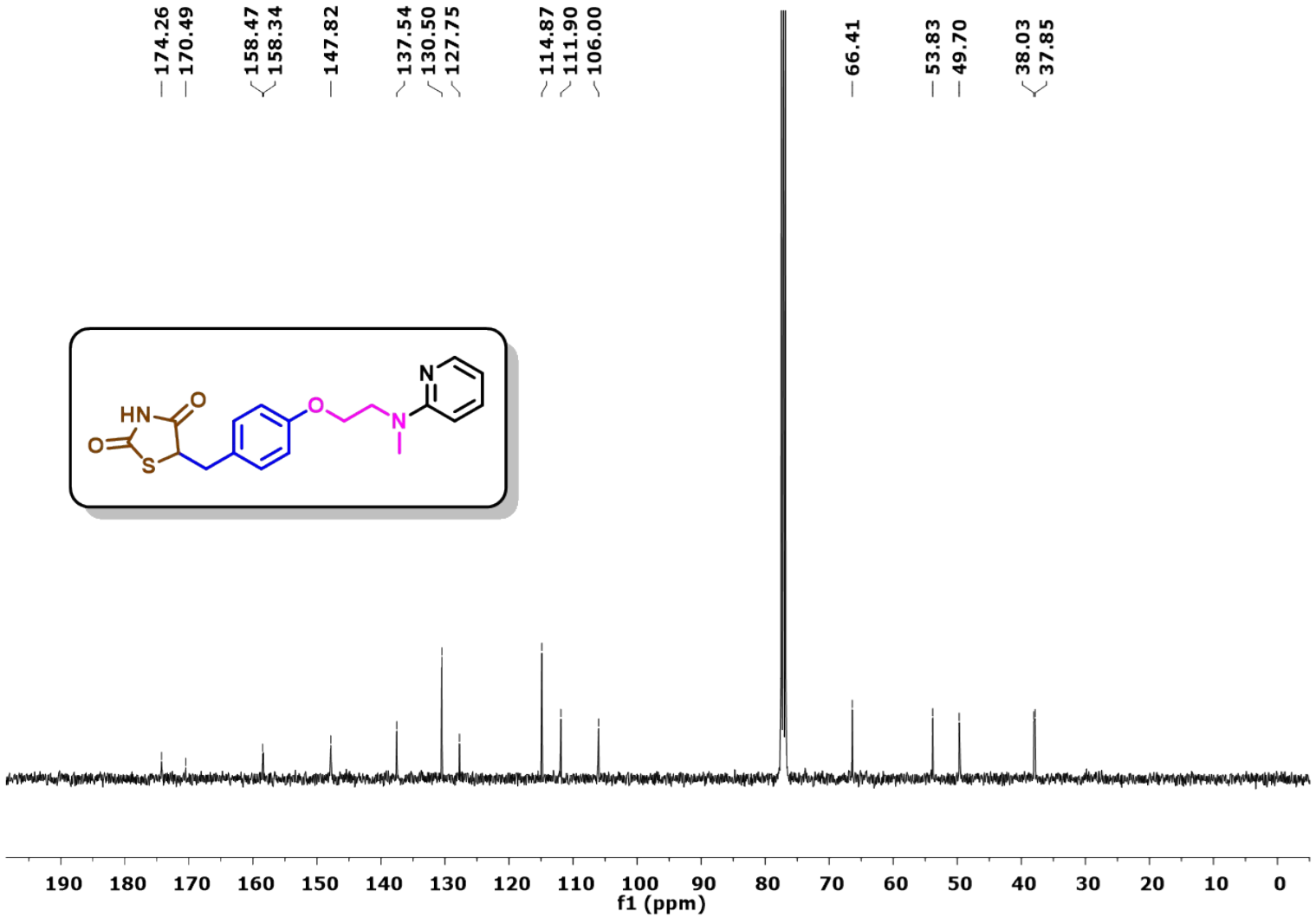


Figure S22. ^{13}C NMR spectra of Rosiglitazone (**9**) in $CDCl_3$ solvent.

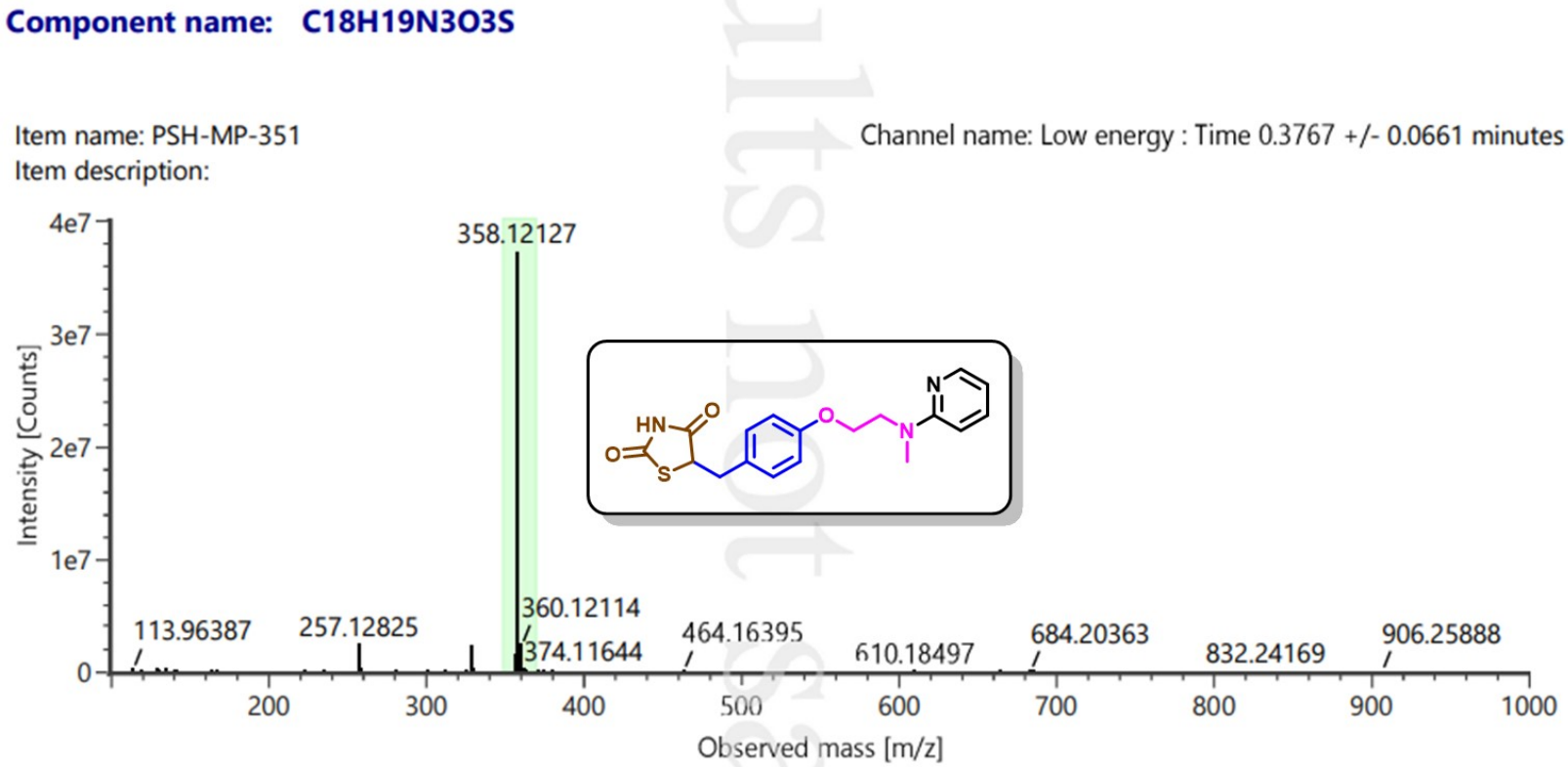


Figure S23. HRMS spectra of Rosiglitazone (**9**).

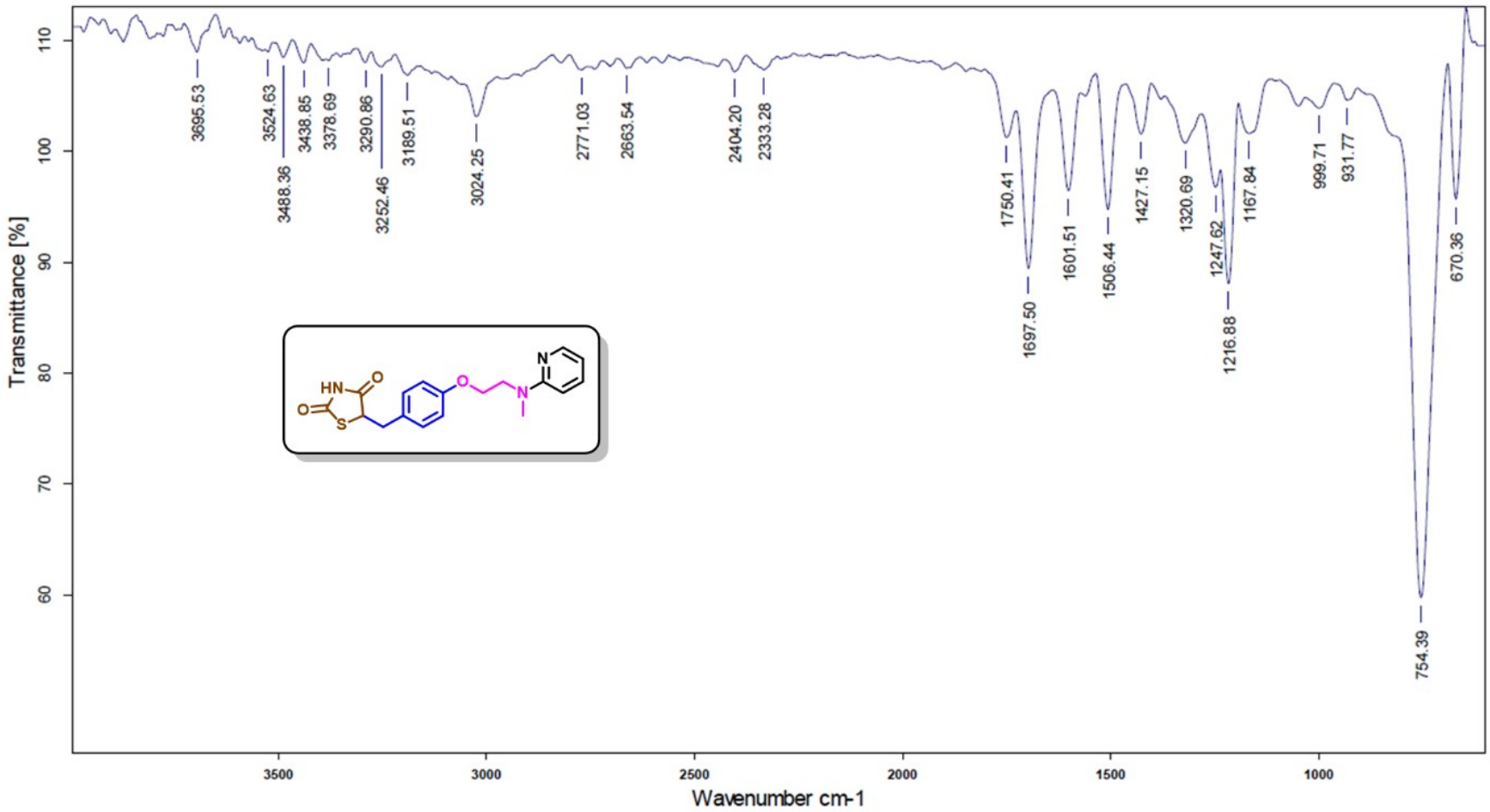


Figure S24. IR spectra of Rosiglitazone (**9**).

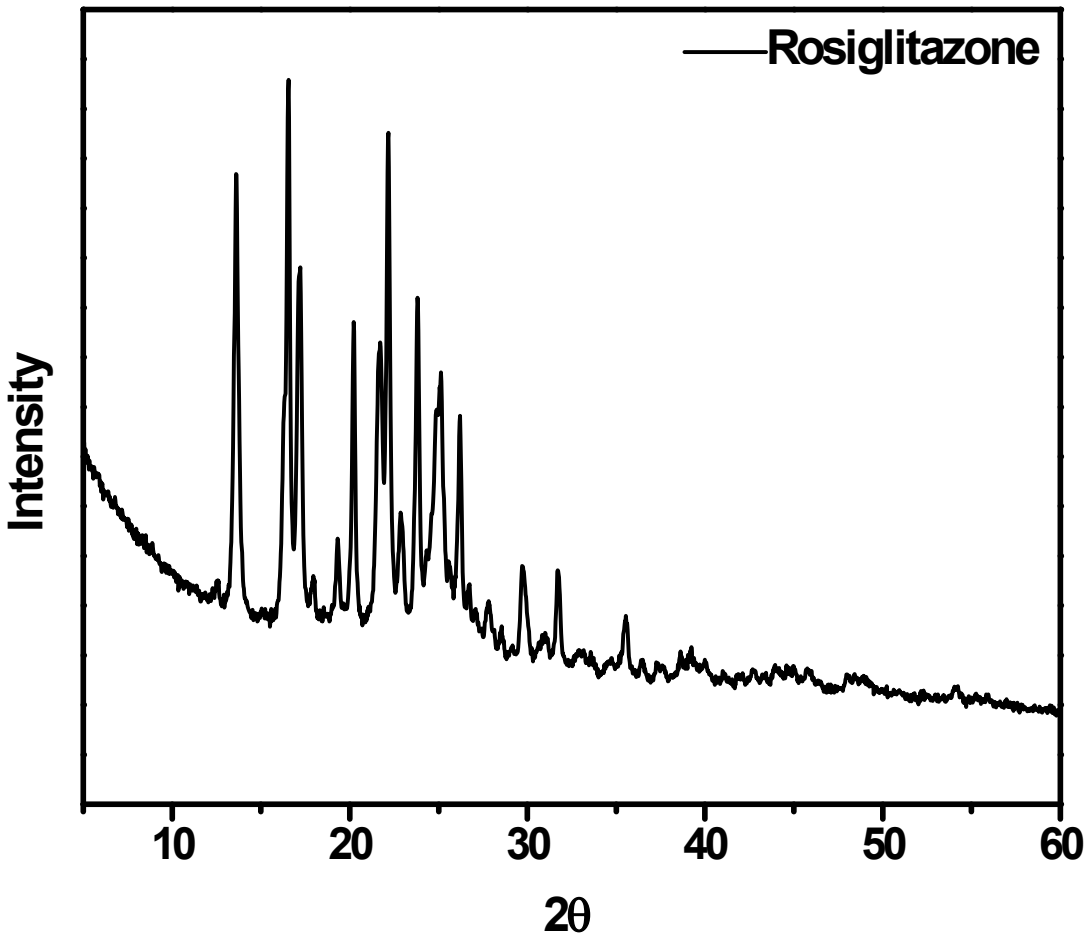


Figure S25. Powder XRD of Rosiglitazone (**9**).

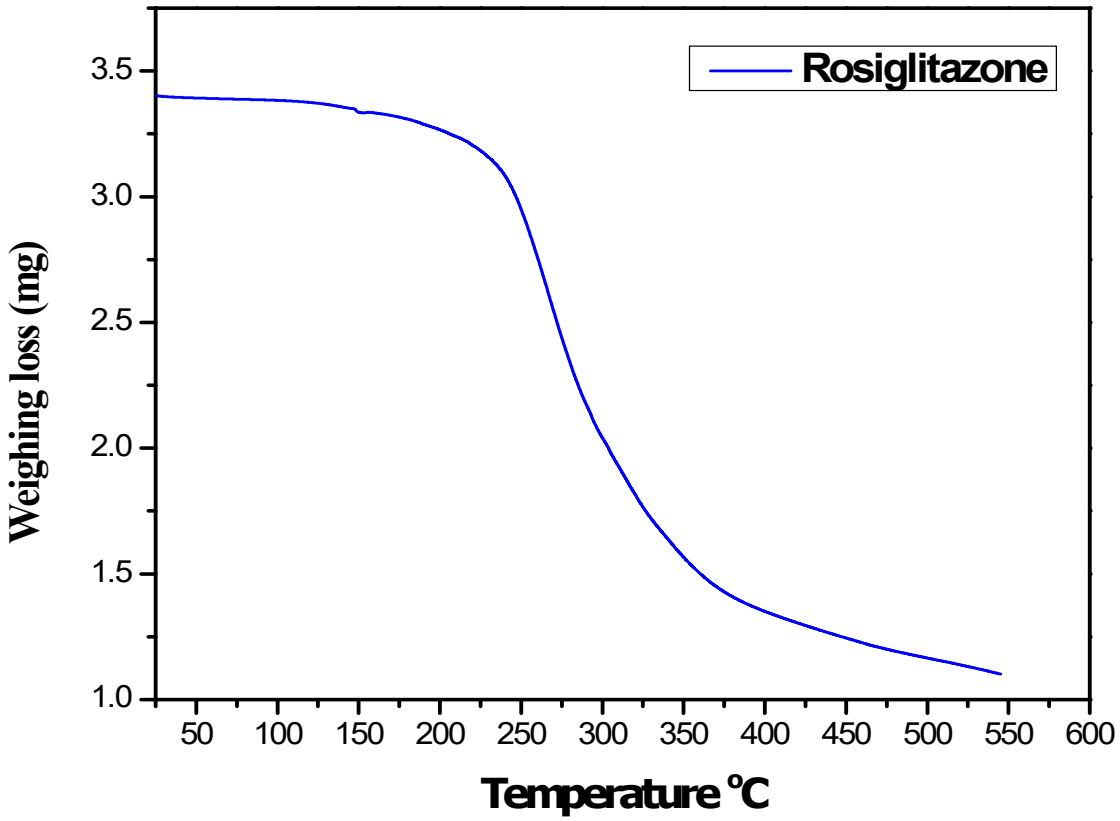


Figure S26. Thermo-gravimetrical analysis data of the Rosiglitazone (**9**).

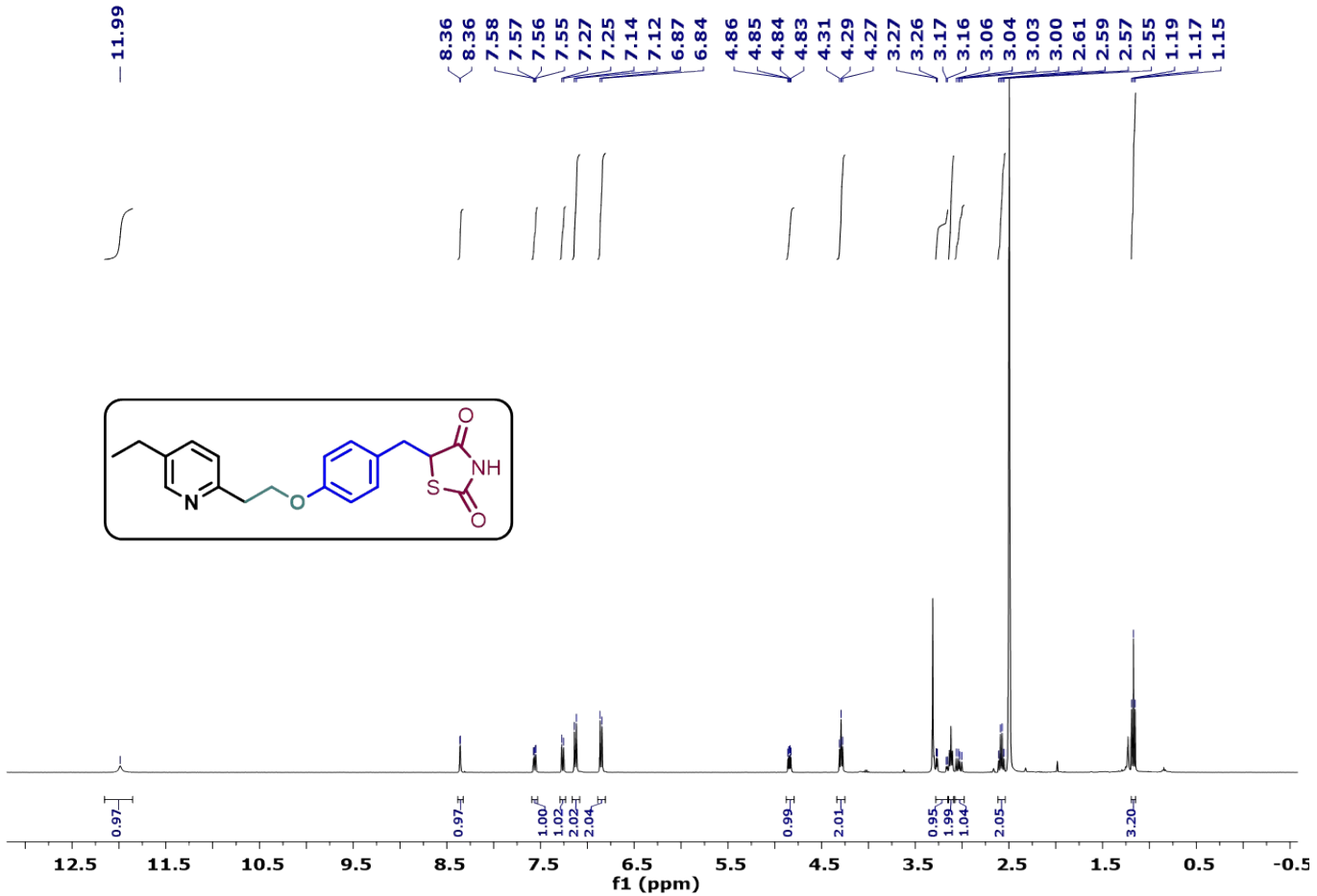


Figure S27. [1]H NMR spectra of Pioglitazone (**13**) in DMSO-d_6 solvent.

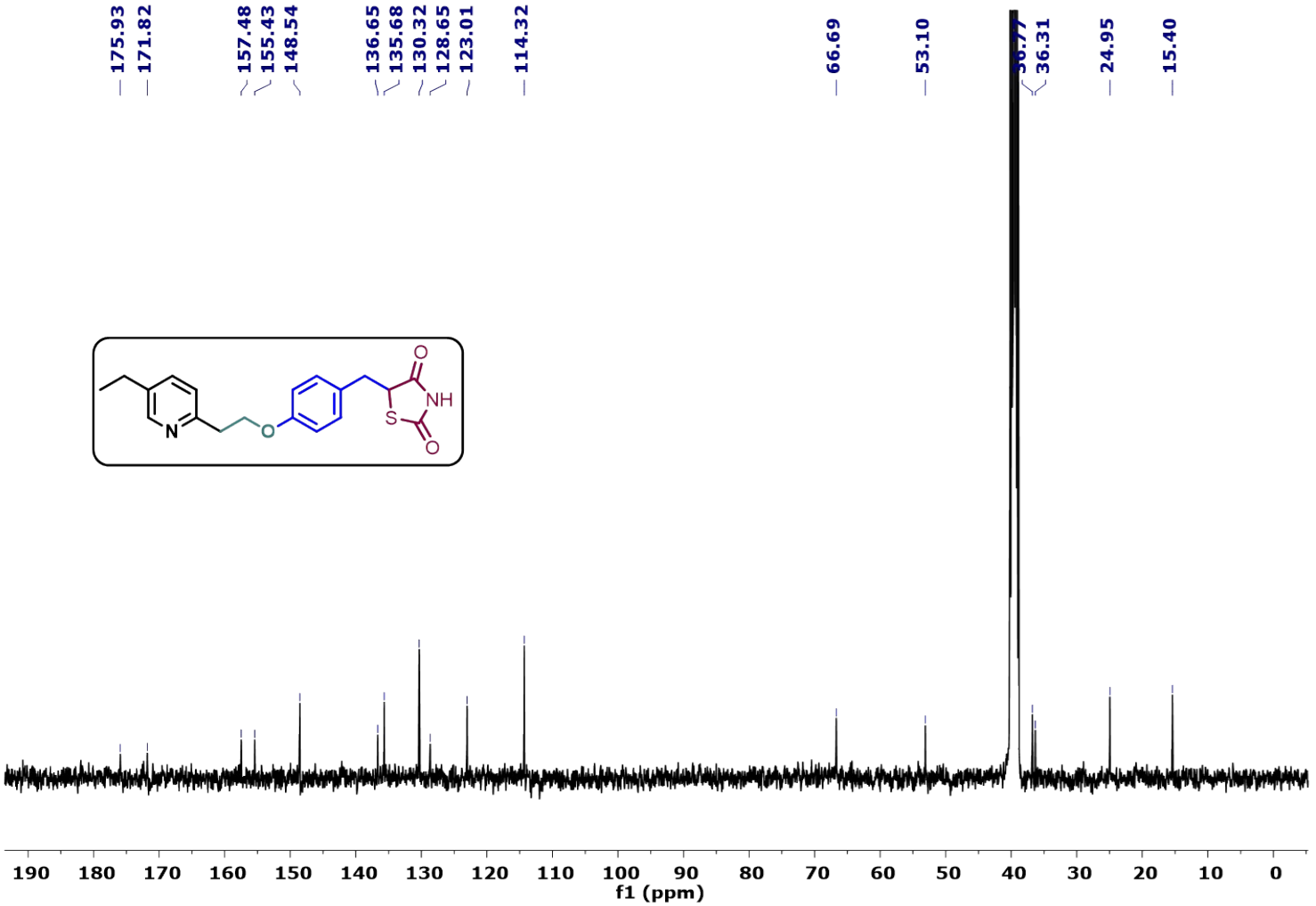


Figure S28. ^{13}C NMR spectra of Pioglitazone (**13**) in DMSO-d_6 solvent.

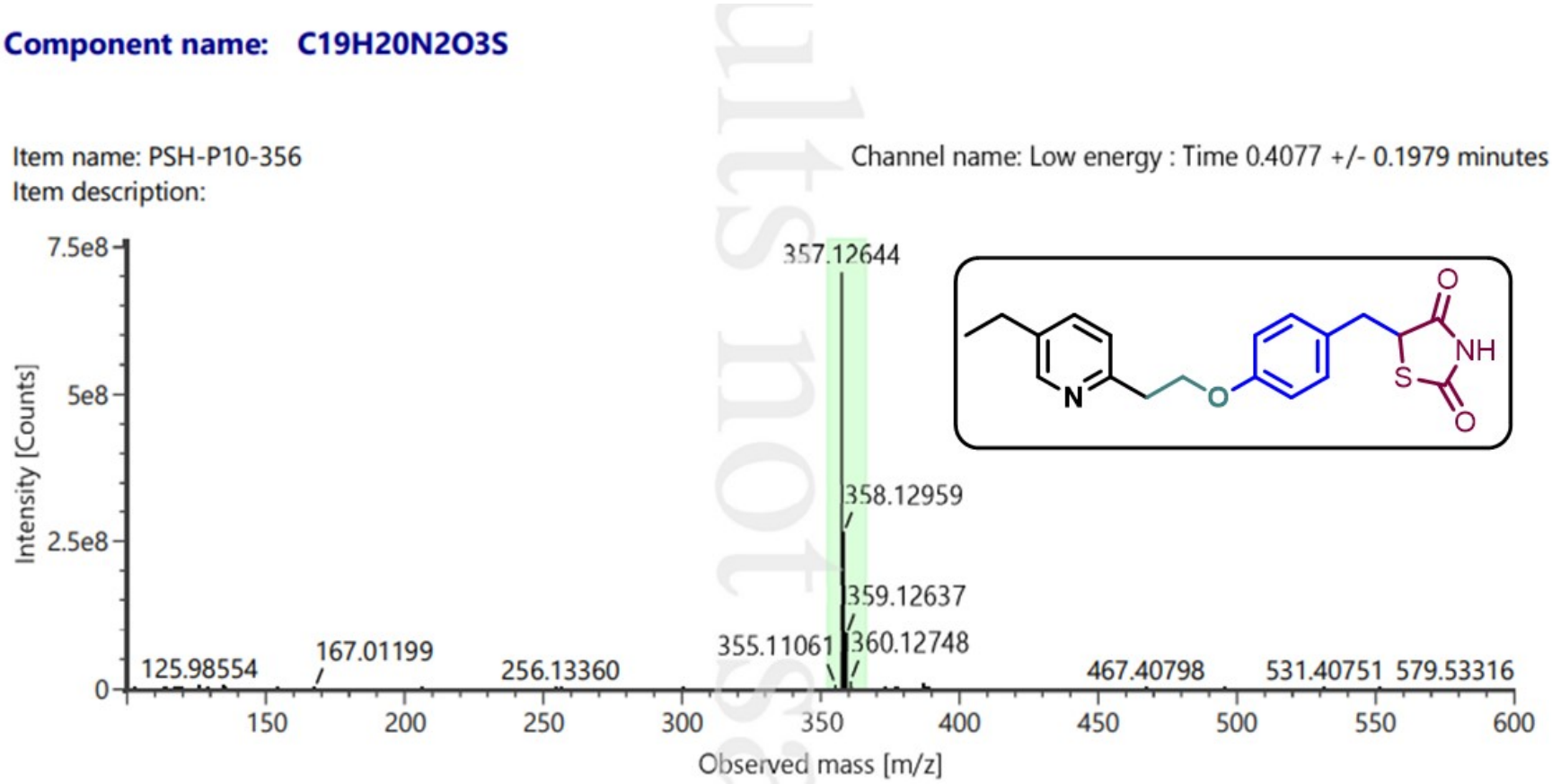


Figure S29. HRMS spectra of Pioglitazone (**13**)

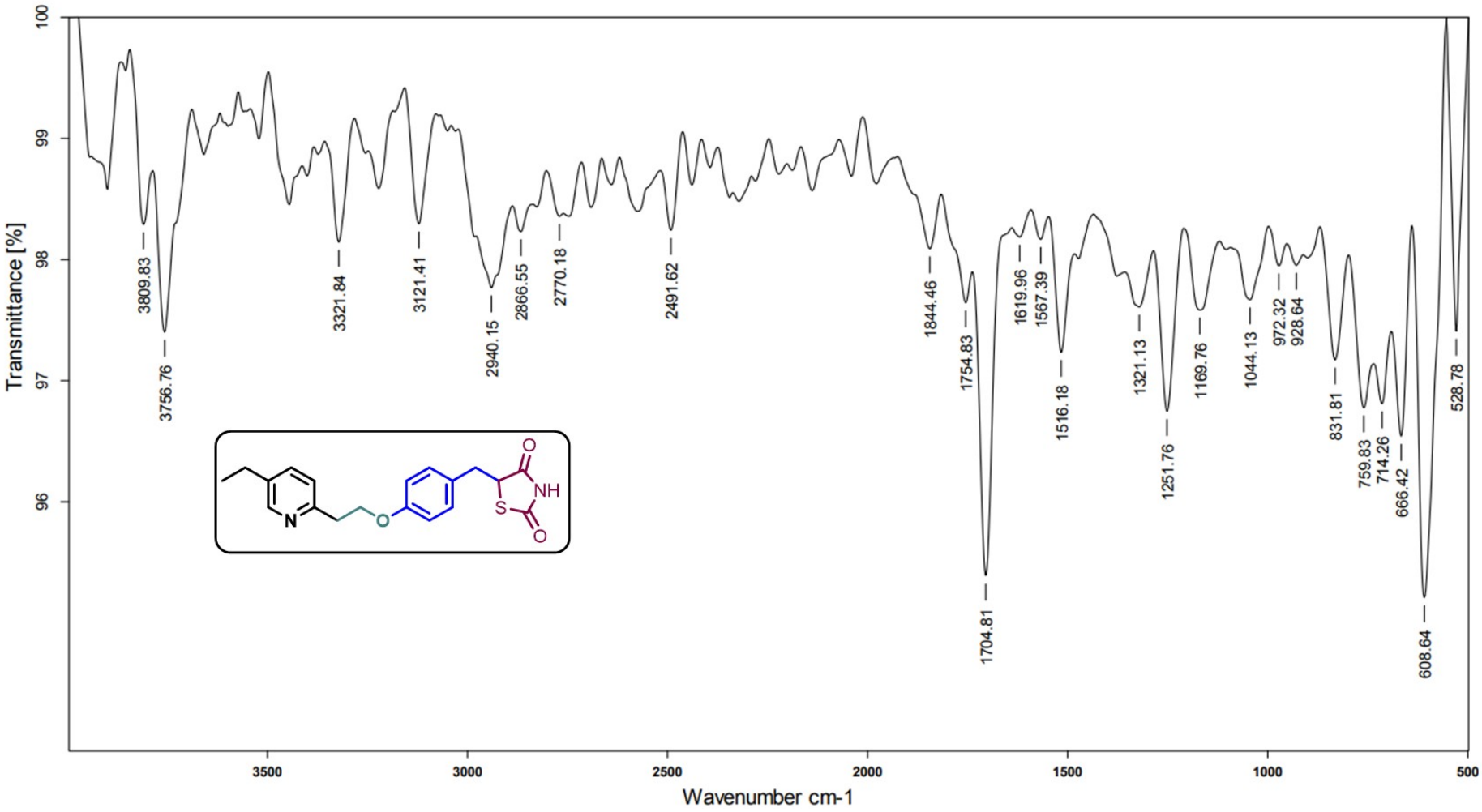


Figure S30. IR spectra of Pioglitazone (**13**).

10. References

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